Life course socioeconomic position, health behaviours and cognitive function in middle-aged and older persons in four Central and Eastern European populations: Findings from the HAPIEE study

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Declaration

I, Pia Horvat, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Identifying risk factors associated with normal cognitive ageing is a prerequisite for understanding dementia. Potential modifiable risk factors include socioeconomic factors and health behaviours. This thesis investigated the importance of life course socioeconomic position (SEP) and two core health behaviours, alcohol consumption and smoking, for mid-late life cognitive function in four previously unstudied Central and Eastern European populations with historically smaller income inequalities and significant contributions of alcohol and smoking to the high premature mortality in these populations.

The thesis used data from over 29,000 men and women aged 45-78 from random population samples in Novosibirsk (Russia), Krakow (Poland), Kaunas (Lithuania) and six Czech towns participating in the HAPIEE study. Cognitive function was measured using four tests of fluid cognition. SEP measures, alcohol consumption and smoking were self-reported using structured interviews.

Structural equation analyses revealed significant associations between SEP measures from across the life course and cognition. Education consistently showed the strongest association with cognition and some accumulation of disadvantage across the life course was observed, similar to studies in Western countries. However, variation in magnitude of these associations across centres may partly reflect the influence of contextual factors.

Regression analyses showed modest associations of cognitive function with alcohol and smoking, and neither of these behaviours appeared to significantly mediate the associations

between life course SEP and cognition. An inverted U-shaped association indicated slightly worse cognitive performance among male heavy drinkers and lower scores in non-drinkers, compared to light drinkers. Binge drinking and alcohol type were not associated with cognitive performance. Smoking was associated with poorer mental speed in both genders but not with any other cognitive test.

The findings suggest a pattern of associations between life course SEP and cognition similar to Western populations and modest associations of alcohol and smoking with mid-late life cognitive performance in these Central and Eastern European populations.

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List of Abbreviations

AD	Alzheimer's disease
BMI	body mass index
CEE	Central and Eastern Europe
CFI	comparative fit index
CI	cognitive impairment
CI	confidence interval
CVD	cardiovascular disease
FSU	Former Soviet Union
GF or GFQ	Graduated frequency questionnaire
HAPIEE	Health, Alcohol and Psychosocial factors in Eastern Europe study
IHD	ischaemic heart disease
SD	standard deviation
SE	standard error
SEM	structural equation model/modelling
SEP	socioeconomic position
MAR	missing at random
MCAR	missing completely at random
MCI	mild cognitive impairment
MI	myocardial infarction
MMSE	Mini Mental State Examination
MNAR	missing not at random
NART	National Adult Reading Test
OECD	Organisation for Economic Co-operation and Development
OLS	ordinary least squares
RMSEA	root mean square error of approximation
RR	relative risk ratio
TLI	Tucker-Lewis index
USSR	Union of Soviet Socialist Republics
WHO	World Health Organization
WLSMV	Mean and variance adjusted weighted least squares
WWII	Second World War

Introduction

The risk of developing dementia rises exponentially with age (1,2). With global population ageing, the public health impact of dementia and cognitive impairment is rapidly increasing in importance (3) and is expected to increase even more rapidly in the future (4). Even in absence of dementia, poor cognitive status and cognitive decline represent a major societal burden and are associated with loss of independence (5), lower quality of life and increased risk of premature mortality (6). There is considerable overlap between decline in cognitive function in and preceding dementia (7,8) and decline in cognitive function, which occurs as part of the normal ageing process (9). Understanding normal cognitive ageing is therefore a prerequisite for identifying risk factors and prevention strategies for dementia (10).

In addition to age and hereditary factors, identification of modifiable environmental and behavioural risk factors associated with cognitive ageing is a first important step towards developing effective interventions and prevention strategies (11). This is best achieved by adopting the life course perspective (10), which recognizes the potential importance of childhood and adult factors as well as life course history in shaping both cognitive decline and the development of cognitive reserve (12). Socioeconomic factors are among the early life and midlife factors which appear to be associated with late life cognitive function (13) and dementia (14). Together with childhood cognitive ability, education attained early in life and adult occupation constitute the main components of cognitive reserve (9,15,16).

Understanding the importance of the different life course stages and the key pathways in the relationship between socioeconomic factors and cognitive ageing would help in developing

effective interventions and prioritizing efforts to reduce socioeconomic disparities in cognitive ageing. One of the hypothesized key pathways is through health-related behaviours. Among the core health behaviours, moderate alcohol consumption (17) and smoking (18) appear to be associated with reduced and increased cognitive risk, respectively. However, several areas of ambiguity remain, reflecting inconsistent findings and lack of focus on drinking patterns, high alcohol consumption, past drinking behaviour and the combined effects of alcohol and smoking on midlife and late life cognitive function. Given the large numbers of people affected, even small reductions or increases in cognitive risk associated with alcohol consumption and smoking may be significant at the population level (10,19). Likewise, even small increases in cognitive reserve resulting from a more equitable distribution of socioeconomic factors, such as education, may have significant implications for cognitive ageing at the population level.

The contributions of socioeconomic factors and health-related behaviours to cognitive ageing have not yet been well studied in Central and Eastern European populations. This may prove to be an important omission. Firstly, these populations are distinguished by historically low income inequalities and, secondly, health-related behaviours contribute significantly to the disease burden and high mortality in Eastern Europe (20). By studying the associations of life course socioeconomic position (SEP) and two core health behaviours, alcohol consumption and smoking, with cognitive function in middle and older age in four Central and Eastern European population samples, this work attempts to fill some of the existing gaps in epidemiologic literature and pave the way for future research in the respective populations and beyond.

This thesis is organized as follows. Chapter 1 opens with a brief overview of general concepts and background topics, before providing a comprehensive literature review. Theoretical perspectives and empirical evidence on SEP and mid-late life cognitive function are reviewed first, followed by self-standing reviews on mid-late life cognitive function with alcohol consumption and smoking as respective exposures of interest. This structure is adopted throughout the thesis. It is anticipated that health behaviours, namely alcohol consumption and smoking, may be important pathways mediating between SEP and cognitive function in middle and older age. However, recognizing the potential importance of alcohol consumption and smoking as independent risk factors for cognitive function, and not just as potential mediators of the association with SEP, this thesis also provides comprehensive investigations of alcohol consumption and smoking in relation to mid-late life cognitive performance. Chapter 2 outlines the major aims and objectives of this work. Chapter 3 describes the data and methodology employed in this thesis. Results are presented in Chapter 4 in separate sections on life course SEP, alcohol consumption, together with a sub-study of former drinkers and past drinking behaviour in Novosibirsk, and, finally, smoking behaviour in relation to cognitive function. Chapter 5 concludes with a brief summary of the findings and a general discussion of strengths and limitations of the thesis, followed by self-standing discussions of the findings on cognitive function with life course SEP, alcohol consumption and smoking as respective exposures of interest, before closing with a consideration of the wider implications of the thesis and possible avenues for future research.

Chapter 1. Background

The first chapter provides the background to the thesis and is organized into two parts. The first part opens with an overview of general concepts and background topics, which underlie much of the research presented in this work, and in the given order provides a description of cognitive ageing, the concept of socioeconomic position (SEP) and its applications in epidemiology, the life course perspective and, finally, trends in mortality, health and social stratification in Central and Eastern Europe (CEE) over the second half of the 20th century and beyond. The second part of this chapter is devoted to a literature review. Theoretical perspectives and empirical research on the relationship between mid-late life cognitive function with SEP, and two core health behaviours, alcohol consumption and smoking, as respective exposures of interest are discussed separately, starting with Section 1.5.

1.1. Cognitive ageing

This section provides an overview of the main concepts in cognitive ageing, which underlie much of the research presented in this thesis.

The focus of research on cognitive ageing has recently shifted to also include normal cognitive ageing (21), not just neurodegenerative disorders, such as Alzheimer's disease and

dementia. This is significant for two reasons. First, normal cognitive ageing affects much larger sections of the population (9). Second, understanding normal cognitive ageing is a prerequisite for identifying risk factors for and targeted interventions for prevention of dementia and cognitive impairment (10).

When studying individual differences in cognitive ageing it is important to distinguish between two factors: initial or baseline level of cognitive function and the rate of cognitive change over time (9). Both the baseline level of cognitive function or peak cognitive performance and the rate of cognitive change over time vary significantly between individuals. The level of cognitive function in later life or peak cognitive performance is strongly associated with cognitive ability in childhood, and has been estimated to have heritability of around 50% (22).

It is well known that most cognitive functions decline with age (23,24). Decline in cognitive capabilities with age in absence of neuropathological conditions, such as dementia and mild cognitive impairment, is a normal aspect of the ageing process (21). Cognitive decline has been detected as early as middle age (25,26), and may be detected even earlier for some cognitive functions (27). However, age-associated decline does not occur uniformly across all cognitive functions (24). Fluid cognitive abilities are most affected. Fluid cognition includes working memory, long-term memory, executive functions, processing speed and reasoning. This is significant because fluid abilities are instrumental for coping with the demands of daily living. Crystallized abilities include acquired knowledge, implicit memory and vocabulary, and are generally not affected by age-associated decline and often remain intact at older ages. Cognitive decline usually occurs in several fluid cognitive domains at once (24), and different fluid abilities may decline at different rates (28). Thus as a result of

different rates of cognitive decline, between-individual differences in cognitive function increase with age (28). This process is accompanied by an increase in within-individual variance as some cognitive functions decline more than others, thereby increasing the gap between best and worst retained functions (28).

An important concept in cognitive ageing research is cognitive reserve. Cognitive reserve is a hypothetical concept, originally conceived to explain the inconsistent association between the degree of underlying neuropathology and its clinical expression (29). The cognitive reserve hypothesis assumes that individual differences in cognitive processes (cognitive reserve) or underlying neural networks (brain reserve) enable some individuals to better compensate for a similar degree of neuropathology than others. For example, cognitive reserve may explain the finding that high education is associated with lower risk of dementia and cognitive impairment (14), assuming a positive relation between education and cognitive reserve. Cognitive reserve may have two kinds of implications for cognitive ageing: it could actively protect from cognitive decline (active model) or increase the initial level of cognitive function (passive model), thereby, raising the threshold for clinical expression of cognitive impairment and dementia.

1.2. Measuring socioeconomic position in epidemiology

The inverse association between socioeconomic position (SEP) and health is one of the most robust and general epidemiological findings. The most widely used definition of socioeconomic position in epidemiology states that it refers to social and economic factors which influence what positions individuals or groups hold within the multiple-stratified structure of a society (30,31).

This view of society stratified by multiple dimensions is generally ascribed to Max Weber, who distinguished between two principal dimensions of social stratification: class and status ((32), also see (33) for a recent discussion). Social class is determined by economic relations and positions within the labour market, whereas social status corresponds to perceived prestige or honour in the community. This process creates groups that share a common position within society and have similar life chances. Weber saw individual agency as having a central role in creating life chances, while he also recognized the role of social structural relations in constraining individual agency. There are many other theories of social stratification; the other classic accounts are based on the works of Durkheim and Marx. In contrast to Weber, for Marx all social relations were rooted in social class, defined in relation to the means of production (34). Compared to Weber, Marx also placed a much greater emphasis on structural constraints, while individual agency was afforded a much more limited role. Most measures and applications of the concept of SEP used in epidemiology implicitly or explicitly draw on Weber's idea of a multiply stratified society (31).

Many different indicators can be used to measure socioeconomic position. Importantly, different SEP measures may be associated with different health outcomes in different ways and through different mechanisms as they capture particular aspects of socioeconomic position (35,36). Not all SEP measures are equally relevant to all stages of the life course. However, various measures of SEP are correlated with one another at any given point in time and across the life course. The strength of these correlations may vary across time and space and this may affect associations between SEP measures and health (37). In addition, differences in social stratification in transitional economies or low and middle income countries, compared to high income countries, may affect the meaning and relevance of SEP measures in a given context. Finally, influences of SEP from several stages of the life course may combine to produce health status or disease risk in adulthood and later life.

SEP measures used in this thesis and their relation to the different stages of the life course are summarized in Figure 1.1. As there are many ways of measuring SEP, only the measures that

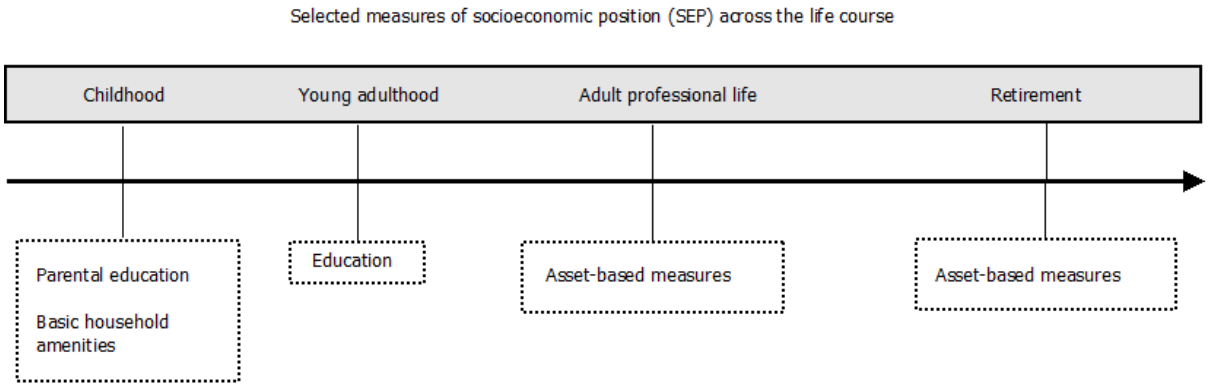

Figure 1.1. Schematic representation of selected life course SEP measures used in the HAPIEE study
The figure shows measures of SEP available in the HAPIEE study and their relation to the different stages of the life course. This representation is based on reference (35), with permission.

are particularly relevant to this work are given consideration in this section. This thesis uses measures of parental education and access to basic household amenities, education, and household asset index as indicators of childhood, early adult and mid-late life SEP.

Education is assumed to measure knowledge and skills-related assets of an individual (35), the so-called human capital in economics. Educational attainment is the first transition from parental to individual's attained socioeconomic position. Thus, education is often used as an indicator of individual SEP in young adulthood or early life in life course research (38), and this interpretation is also adopted in this thesis. Educational attainment has been seen as a function of educational opportunities in a society as well as parental socioeconomic position and parental aspirations. In most contemporary societies education is a significant determinant of adult occupational attainment and adult earnings. Earnings of the more educated are almost always above average, although returns to education tend to be higher in low and middle income countries than in high income countries (39). Education-based measures of SEP have several advantages, which include ease of measurement using self-reported questionnaires, typically high response rates, and applicability to all adults, irrespective of age and employment status.

Asset-based indices are used to measure inequalities in household living standards (40), and may be used as proxy measures in absence of household income or consumption expenditure data or in conjunction with other measures of socioeconomic position. Asset-based measures typically collect information on ownership of a range of durable assets, such as car, refrigerator, and television, and may also collect information on housing characteristics and access to basic services. This information is then used to construct an index. There are several potential advantages of using asset-based measures to classify socioeconomic position

of households. First, asset indices are generally a more stable indicator of material circumstances than income (40). Second, asset-based measures tend to give higher response rates and better accuracy and validity than questions on income or expenditure. Finally, asset data are less likely to be affected by reporting bias and may be more informative in contexts, where informal economy is widespread, such as transitional economies or low and middle income countries (41). A significant limitation of asset-based measures is that they capture relative social position and cannot be used to measure absolute levels of SEP or poverty. In addition, information on ownership of generic assets is typically collected, irrespective of their quality, although higher socioeconomic position is thought to be positively associated with higher asset quality. Furthermore, consumers may also be sensitive to perceived social status associated with ownership of some assets, for example, car, and thus such assets may be less reliable indicators of actual living standards.

Childhood SEP is typically measured using parental characteristics. Father's occupation is thought to represent the socioeconomic dimension of the family's social position. Father's occupation has commonly been used in health research and is generally considered a more powerful indicator than mother's occupation, given historically low rates of female labour participation. Parental education is thought to reflect the cultural dimension of the family's social position, sometimes called cultural capital. In addition, measures of family income, household material conditions, such as access to basic amenities, or material hardship are commonly used as indicators of material living standard in childhood or childhood poverty.

1.3. Life course epidemiology

Cognitive function in mid and later life is the sum of genetic and environmental influences from across the lifespan (9) and is increasingly coming to be viewed from the life course perspective (12,42). Life course epidemiology has been defined as the study of long-term effects on later health or disease risk of physical or social exposures during gestation, childhood, adolescence, adulthood and later life (43,44).

A particular contribution of the life course perspective in epidemiology is that it distinguishes between several conceptual models. There are three basic types of life course models with several varieties, as shown in Figure 1.2. adapted from Kuh and Ben-Shlomo (44). First, the critical period model assumes that exposures which occur during a vulnerable developmental phase of life result in irreversible changes to body system structure and function with long-term consequences for health. The timing of exposure is critical. An extended version of this hypothesis maintains that exposures which occur during sensitive developmental periods have large, although not necessarily irreversible, effects on health but may also have smaller effects outside these sensitive periods. This may be especially relevant for socioeconomic exposures and health behaviours, which are likely to have some effect on health throughout the life course, although for certain outcomes their effects may be stronger at particular life course stages.

Second, the accumulation model maintains that exposures or protective factors accumulate across the life course and increase the risk of ill-health or the probability of good health (44). As time spent in adverse conditions increases, so does the risk to health and vice versa for

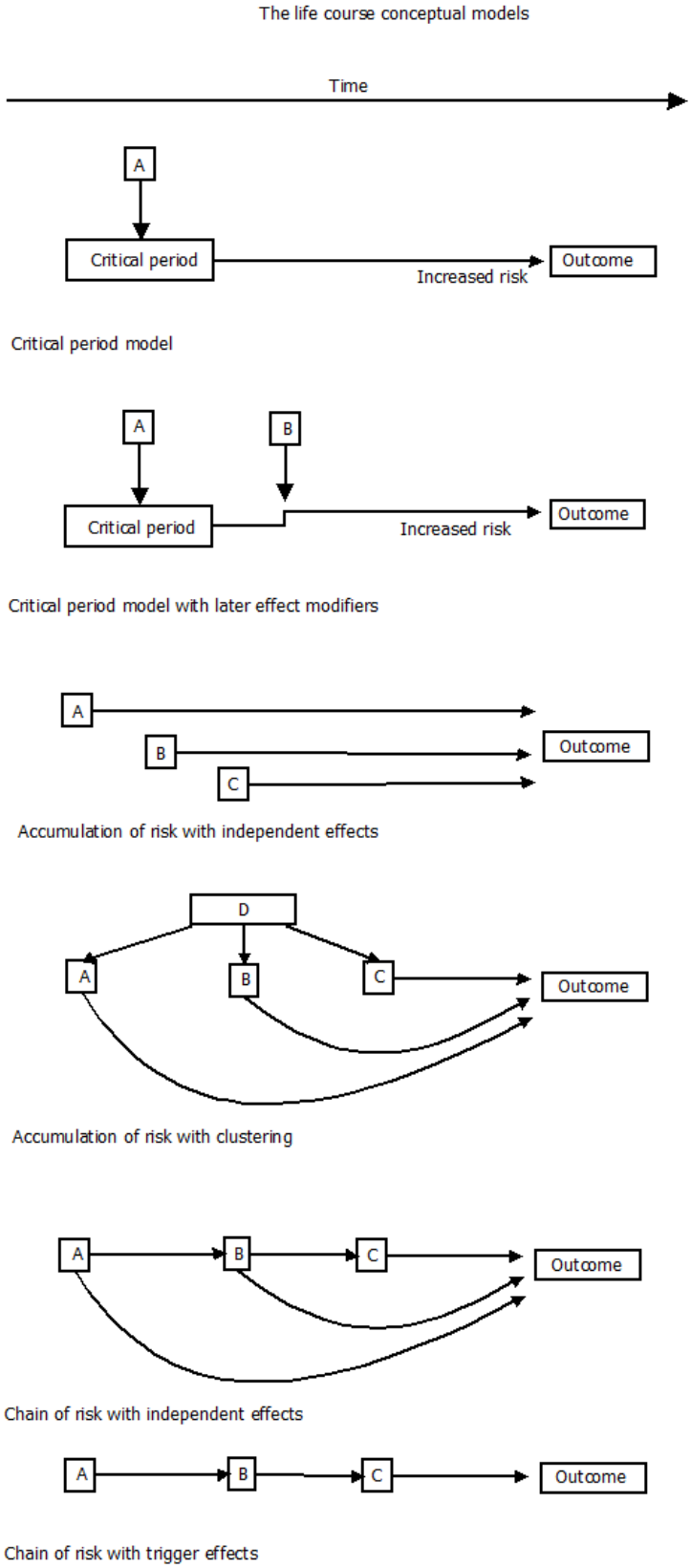

Figure 1.2. Schematic representation of conceptual life course models
Squares A, B, C represent exposures (risk or protective factors) occurring at a point in the life course. Single-headed arrows represent directional effects, connecting exposures with the health outcome. Reproduced in modified form with permission from reference (44).

time spent in advantageous conditions. The pathway model is sometimes considered to be a special case of the accumulation model. In this model initial exposures increase the risk of subsequent exposures, while they may also have independent effects on the outcome. In some versions of this hypothesis, accumulation of disadvantage or advantage across the life course results in a divergence in health and well-being in later life (45) or leads to persistent inequalities (46). In this way, low SEP at any point in time increases the chance of experiencing low SEP at the next point. In addition, socioeconomic risk factors as well as poor health behaviours also tend to cluster together at any given point in time.

Finally, the social mobility model maintains that upward or downward social mobility can modify the association between an earlier exposure and later health outcome.

The significance of these conceptual models is that they allow for an explicit representation of the pathways linking exposures to health outcomes, which may occur years or decades after the occurrence of exposures, and that they account for logical or hypothesized temporal and causal relationships between exposures and outcomes (38).

1.4. Central and Eastern Europe

This section discusses the significance of the Central and Eastern European context of this thesis. First, recent trends in health and mortality in Central and Eastern European populations and their potential explanations are briefly reviewed. Second, the unique socio-historical context and recent societal transformation of Central and Eastern Europe and their relevance for the health and mortality of middle-aged and older persons in these respective populations are described.

1.4.1. Mortality and health

Even today the heath gap continues to divide Western Europe and the formerly communist countries of Central and Eastern Europe (47,48). Life expectancy is, on average, higher in Western Europe than in Central Europe and, especially, in Eastern Europe, particularly in males (48,49). Within the region, life expectancy has been improving steadily in Central European countries since the fall of communism, while in the former Soviet Union (FSU) countries improvements in life expectancy have begun later and been less sustained (48–51) . Understanding the causes of the health gap is important because similar risk factors may contribute to both within and between country differences in health and mortality.

Origins of the health gap are partly historic. The traditionally high mortality in Central and Eastern Europe improved dramatically in the 1950s, owing largely to improvements in control of infectious disease, reductions in infant mortality and to the establishment of new

national health care systems (52,53). However, in the 1960s, 1970s and 1980s total mortality stagnated or increased and these negative trends converged throughout the region (54). The only exception was a short-lived improvement in mortality in the Soviet Union countries in the wake of Gorbachev's anti-alcohol reform (1985-1987) (47,50). In contrast, in Western Europe life expectancy was rising steadily over this period, resulting in an ever greater health gap. The high mortality in the region was largely attributable to deaths from cardiovascular disease and external causes, which were rising among working-age men (52,53,55). Among other things, health care systems in these countries were ill-equipped for coping with cardiovascular and other non-communicable diseases.

After the fall of communism, mortality trends diverged increasingly between the former Soviet Union countries and Central Europe. Trends in male and female life expectancy since 1989 in selected Central and Eastern European countries are shown in Figure 1.3. With few exceptions, life expectancy increased steadily in Central Europe, including the Czech Republic and Poland (52,56). However, life expectancy in the former Soviet Union republics deteriorated significantly (57).

Notably, throughout the 1990s Russia experienced pronounced and unprecedented fluctuations in mortality brought about by transitional economic crises, resulting in a dramatic fall in male life expectancy (54,57), as seen in Figure 1.3. In contrast, life expectancy in the Baltic countries improved slowly at the end of the decade.

In addition, socioeconomic differentials in health and mortality, which were already present under communism (58), increased during the transition (52,59,60) . This trend has reportedly been worse in former Soviet Union countries than in Central Europe (60,61). Education-

related inequalities in mortality generally also appear to be higher in Central European countries and, especially, Baltic countries than the European average, and are partly explained by higher inequalities in CVD and smoking-related mortality and, in the Baltic countries, alcohol-related mortality (62).

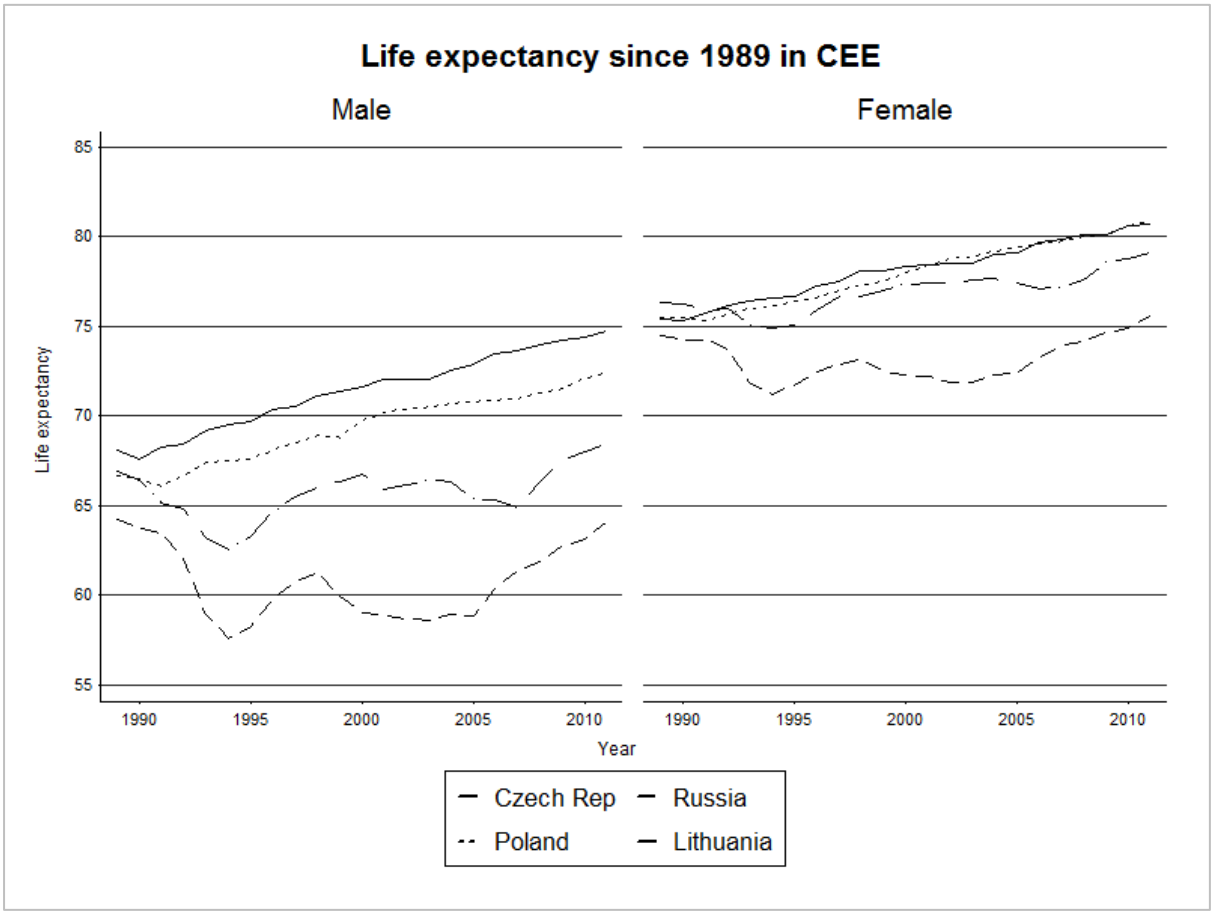

Figure 1.3. Trends in male and female life expectancy at birth since 1989 in selected CEE countries
Source: TransMonEE database (63).

The progress in life expectancy that has been achieved since the fall of communism in Central Europe, and to somewhat lesser extent in the Baltic countries, is significant but as improvements have also continued in the West the gap has proved difficult to eliminate (49).

More recently, improvements in mortality have been seen in all former Soviet Union countries of Europe, including Russia (49). Despite this, life expectancy in Russia remains low by most standards - it was 63 years in 2009 for men (64) -, and it remains unclear whether improvements in Russia and the Baltic countries will be sustained (50,51).

Alcohol and smoking are among the key factors linked to higher mortality in Central and, particularly, Eastern Europe (20,47,48,65,66) as well as, in the case of alcohol, to the transitional mortality crisis in Russia and other FSU countries (67,68). It has been suggested that a significant proportion of premature deaths among working-age men in Russia are attributable to alcohol-related causes (20,67,69), and this is reinforced by a plausible link between alcohol and increased risk of cardiovascular death (70–72). In addition, rates of smoking and smoking-related mortality, particularly from cardiovascular disease, are high in Central and Eastern Europe (66). For example, in Russia the already very high prevalence of smoking in men continued to rise during the transition and increased notably in women from previously low levels (73). There is little doubt about the importance of alcohol and smoking as immediate determinants of mortality in CEE. However, at the distal level social and economic factors almost certainly made significant contributions to the health gap and its development since the fall of communism (74,75).

Since the higher mortality in Central and Eastern Europe and rising mortality during the transition have been largely concentrated among working-age men, this group has been the focus of most empirical research. The health of older people in Central and Eastern Europe is only now becoming the subject of epidemiological research, despite the considerable health burden associated with the region's ageing population (76). The higher mortality, particularly from cardiovascular disease, in Central and Eastern Europe in much of the second half of the

20th century and the potential overlap between its determinants and risk factors for cognitive and physical functioning in older age suggest that rates of poor cognitive and physical functioning might also be expected to be higher in much of the region compared to Western Europe (77). For example, on average healthy life expectancy at 50 years is lower in Baltic and Central European countries than in most Western European countries (78).

Currently there is a notable lack of data on ageing-related outcomes in Central and Eastern Europe, with the available data showing significant variability between Central and Eastern European populations (77). Recent estimates of cognitive impairment and frailty in a Russian urban sample aged 65+ were not dissimilar to other populations, although direct comparisons were not conducted (79). However, other studies have observed greater declines with age in healthy life expectancy (80) and both cognitive (81) and physical (82) functioning in Russia than in Central and Eastern European and/or Western European comparison countries, which may partly stem from greater disadvantage experienced by the Russian population throughout the life course.

While the overlap between immediate determinants of mortality and ageing-related outcomes is likely to be significant, it is also worth noting that, with two unique types of social change occurring in less than half a century, Central and Eastern Europe is particularly well suited for the study of social factors and their association with health and ageing (77). However, thus far few studies have been able to examine social inequalities in ageing related-outcomes and associated risk factors in Central and Eastern Europe. Previous analyses of HAPIEE data documented strong inverse social gradients in the prevalence of functional limitations, and these were largely unexplained by differences in alcohol and smoking behaviours (83). With this in mind, this thesis aims to add to the existing literature by

investigating the contributions of alcohol and smoking and life course socioeconomic inequalities to cognitive functioning in four Central and Eastern European populations.

1.4.2. Social stratification and social change

Two historically unique types of social change have taken place in Central and Eastern Europe in the second half the 20th century: transition to communism and post-communist transformation to the market economy and political democracy (84).

After the WWII communist regimes became established throughout the region, and serious efforts were made to minimize material inequalities between the different social groups and improve the position of workers and peasants. Since the fall of communism there has been a reversal of this trend in most countries of Central and Eastern Europe, accompanied by notable increases in social and income inequalities (85). In this section, trends in income inequality and educational inequality in Central and Eastern Europe since WWII are described. Income inequality is an overall indicator of the distribution of wealth among individuals and groups within a society with potentially important implications for health (86), and access to education is one of its key determinants in developed societies.

1.4.2.1. Income inequality

In socialist countries wages were determined by the central planning mechanism, and influenced by Communist regimes' commitment to providing an egalitarian distribution of

income. The earnings structure reflected industry and occupation preferences, favouring particularly the manufacturing and construction industries, and manual labour relative to professional occupations. As a result the distribution of earnings was more condensed (87) and returns to education were lower compared to countries at similar levels of development (88), and generally also lower compared to contemporary capitalist countries, or at least at the low end of the spectrum (89).

Abolishment of private ownership greatly limited opportunities for accumulation of wealth and its intergenerational transmission through inheritance, compared to Western countries (90,91). In capitalist countries inheritance of wealth has been a crucial mechanism in the reproduction of socioeconomic inequalities. Female labour participation at all ages was much higher in socialist compared to market economies, and this resulted in greater equality of personal incomes.

Findings of Western scholars on the level of income inequality in communist Central and Eastern Europe in comparison to contemporary Western countries have sometimes been contradictory. Bergson (91) found that in the 1970s earnings inequality in the USSR was only slightly lower than in the West. In contrast, McAuley (92) concluded that USSR achieved considerable reductions in earnings inequality and had a significantly more equitable income distribution than Great Britain, USA or Italy in the 1960s, while noting that poverty was still widespread.

Flemming and Micklewright (90) (echoing previous findings by Atkinson and Micklewright (93)) observe that variation in the distribution of income was significant between socialist countries and within socialist countries over time, and that temporal variation of this kind is

characteristic of most societies. They conclude that in the late socialist period earnings inequality in Central European countries was at the low end of the range observed in Western countries, whereas in Soviet Russia it was already well within that range. Notably, Czechoslovakia had a very low and relatively stable earnings inequality throughout the socialist period (90,93,94), which was determined largely by gender and age rather than education like in Western countries (94). Poland had a higher and more variable earnings inequality than Czechoslovakia, while earnings inequality in the USSR was one of the highest among socialist countries and showed considerable variability over time (90). Similar patterns were observed for income inequality (90,95). Czechoslovakia was the most equal and USSR the least. In the mid-1980s income inequality was just below the OECD range in Czechoslovakia, while Poland and Russia were significantly more unequal than the most equal OECD country but on par with other Nordic countries.

Thus, it appears that income inequalities in communist Central and Eastern Europe were certainly lower than in countries at similar levels of development (96), and in some socialist countries, such as Czechoslovakia, income inequalities were low by most standards (93). However, with the fall of communism income inequality and poverty levels increased significantly in all Central and Eastern European countries (85). The increase in income inequality has been the sharpest in the FSU countries and much more contained in Central European countries (95,96). In Russia the level of income inequality reached the levels typically seen in Latin America by mid-1990s and wage inequality reached a level higher than that of the US (97).

In the same vein, returns to education, a significant determinant of wage inequality, increased during the transition in most countries from previously low levels (87,96,97) but in the 1990s

were generally still below the average returns for middle income, developing countries (88,97,98).

1.4.2.2. Educational inequality

Communist regimes were concerned with creating a greater equality of educational opportunity, particularly in favour of children from disadvantaged backgrounds. Serious efforts were made to eliminate the influence of economic resources on access to education. Education was provided free at all levels, fees and private schools were abolished, and stipends for children from disadvantaged backgrounds were widely available (99).

Achievements have been made in reducing social origin-based educational inequalities in most countries of the region. Dramatic educational expansion and efforts to modernize the education system notably increased educational participation, and enrolment levels attained were much higher than in countries at similar levels of economic development (100). Educational opportunities, particularly at vocational and secondary levels, improved for children of working class and peasant families (101,102). The effect of parental background on final educational attainment has declined over the period (103) and weakened from the pre-communist period (104). Gender inequality in education was also almost completely removed or even reversed (105).

Despite widespread measures to reduce educational inequality and some notable achievements, socialist educational stratification showed the general characteristics typically found in Western capitalist societies (100). Socioeconomic background remained a

significant influence on educational attainment throughout the socialist period in all countries studied (101,102,106,107). Improvements in educational inequality were generally linked to educational expansion and industrialisation rather than specific socialist policies (101–103,107,108). Comparison of educational inequalities in five Eastern European countries, including the Czech Republic and Poland, showed that the effects of parental background on final educational attainment have declined over the socialist period, most likely as a result of educational expansion, but continuation probabilities at schooling transitions changed little (103). In the Czech Republic support was found for the 'socialist transformation' hypothesis, which predicts a decreasing impact of family background on educational attainment at the onset of communism but no further weakening or a re-strengthening of this relationship once a new socialist elite and social structure crystalize (102). Finally, in Soviet Russia the rapid expansion of secondary education favoured children from disadvantaged backgrounds, but this group also appears to have been disproportionally hurt by the lagging growth of tertiary schooling and increasing social inequality in access to higher education (101).

Notwithstanding the broadly similar patterns of educational inequality in socialist Europe compared to Western countries, the relative weight of the different mechanisms generating it may not have been the same as in Western capitalist countries. It has been suggested that socialist societies may have been more meritocratic than many capitalist societies (99,101,109), since differences in educational attainment would be expected to reflect differences in ability relative to differences in socioeconomic resources to a greater extent. In addition, given the limited opportunities for gaining material advantage and transmitting it to ones' children, parental cultural capital may have been more important than socioeconomic factors in the intergenerational transmission of educational advantage (108). For example, a study found weaker effects of father's occupation on offspring's educational attainment and

slightly stronger intergenerational educational reproduction in formerly communist countries compared to non-communist countries (110).

Finally, in socialist Central and Eastern Europe education had high cultural significance but relatively low economic returns due to wage equalization policies. This may have partly counteracted the efforts aimed at improving educational access for children from more disadvantaged backgrounds with traditionally lower educational aspirations, since additional qualifications may not have been needed to attain desired earnings, and this process may have been exacerbated by heavy vocational emphasis in secondary education (102).

In summary, it seems that despite significant efforts and some notable achievements educational inequality under communism was not markedly lower than in contemporary Western countries (102,110), although it may have been partly the result of different underlying processes. However, economic returns to education were significantly lower in CEE than in Western countries.

1.5. Socioeconomic position and cognitive function

Building upon the background concepts and topics reviewed in the first part of this chapter, the second part of this chapter is devoted to a literature review. First, Section 1.5. reviews theoretical perspectives and empirical research on socioeconomic position and mid to late life cognitive function. The theoretical and empirical relevance of childhood SEP, education and adult SEP to cognition are evaluated separately, before the section concludes with a review of life course studies.

1.5.1. Childhood SEP

Consistent with the life course approach is the expectation that early childhood experiences may have long-lasting consequences for cognitive health (111). Enduring effects of childhood SEP on cognition could partly reflect the association of childhood SEP with early life cognitive development (112), and there are several plausible pathways for this association, including maternal exposures during gestation, maternal and early life stress exposure (113), maternal and early life nutrition, intrauterine and postnatal growth (114), childhood health, parenting practices (115), mental stimulation and environmental enrichment in childhood, and material deprivation.

Early years are crucial for brain development, and it is conceivable that adverse effects of early life insults on cognitive function become exacerbated with cognitive ageing (116). Cognition is also most environmentally plastic in early life with heritability of cognitive

ability rising from a low value of between 30-40% in early childhood to over 50-60% in adulthood (22,117). In addition, socioeconomic background may modify the heritability of childhood cognitive ability, and environmental influences appear to be more important at lower levels of SEP (118).

Thus, it is plausible that intrauterine and childhood exposures associated with SEP have independent long-lasting effects for cognition. Whalley, Dick and McNeill (111) identify three possible pathways that could link foetal development with dementia and these pathways may also apply to normal cognitive ageing. They suggest that insults during foetal development may: 1) directly affect brain structure and function with implications for cognitive health in later life, 2) accelerate the rate of cognitive and/or physical ageing, or 3) indirectly affect cognitive ageing through cardio-metabolic factors in adulthood.

The third pathway identified by Whalley et al. (111) suggests a primarily indirect effect of childhood factors on late life cognition, mediated by adult factors. Notably, childhood SEP also influences future life chances and adult socioeconomic attainment. Children from disadvantaged backgrounds are more likely to receive a low quality diet, poor medical care, live in low quality housing and have few educational opportunities. These, in turn, limit employment options and negatively affect future income trajectories, leading to fewer resources in adulthood. According to the cumulative advantage and disadvantage perspective (CAD) (45,119), in this way social inequalities in health are initiated early in life and increase with age as initial advantages or disadvantages accumulate and compound across the life course, leading to persisting inequalities or a divergence in health and well-being in later life.

Cross-sectional studies with retrospective measures of childhood SEP have shown positive associations between childhood SEP and better cognitive performance in mid or later life (120–124), as well as Alzheimer's disease (116) and dementia (125). The associations of childhood SEP with cognitive performance were partially mediated through later SEP measures, since the effect of childhood SEP was consistently attenuated after adjusting for later SEP measures. Relatively weak residual associations remained between childhood SEP and mid or late life cognitive function in some studies of cognitive performance (120,121), while the associations were stronger in other studies (122,123).

Birth cohort studies, which benefit from longitudinal design, have identified cognitive development as another important factor mediating the association of childhood SEP with mid and late life cognitive function (126–129). In these studies the associations between childhood SEP measures and cognition were mediated by childhood cognitive ability and partially by education and adult SEP. However, in the 1953 birth cohort of Danish conscripts (127) father's social class was not only significantly associated with cognition measured at ages 12 and 18 but also showed a modest independent association with cognition at age 57 in a model controlling for education, adult SEP and adolescent cognitive ability. Similarly, in the 1946 British birth cohort (129) the association between childhood material deprivation and midlife cognition was largely explained by adjusting for childhood cognitive ability and adult SEP but childhood adversity remained independently, although weakly, associated with mental speed.

In addition, two cross-sectional structural equation analyses evaluated indirect associations between retrospectively reported measures of childhood SEP and midlife or late life cognition. In the Chicago-based Rush Memory and Ageing Project (130) the total effect of

childhood SEP on late life cognition was larger than the direct effect of adult SEP. The effects of early life SEP were fully mediated by a combination of adult SEP measures and premorbid cognitive ability. However, in this study the model also included childhood cognitive activities, such as the frequency at which the child was read to and played games with, which were significantly associated with both midlife cognitive activities, such as frequency of reading and attending cultural events, and late life cognition. A similar conclusion was reached by a study of British civil servants, which found that the indirect effects model of childhood SEP provided a better description of the data than the direct effects model (13).

In these studies childhood SEP was typically measured as an index combining information from several parental or household indicators (e.g. (120,121)). In addition, Kaplan et al. (121) also examined independent contributions of different parental measures in middle-aged Finnish men; they found that mother's education was directly associated with midlife cognitive function, whereas the effect of father's occupation was entirely mediated through participants' own education. In this study, the effects of father's occupation were fully explained by its influence on offspring's education, which was, in turn, associated with midlife cognition. On the other hand, mother's education could reflect more subtle factors associated with cognitive development, such as prenatal growth or childhood cognitive milieu, which were not fully accounted for by later SEP. Similarly, in the Health and Retirement Study (122) mother's education also showed the strongest association with late life cognitive performance and self-reported memory problems among childhood SEP measures. This suggests that different mechanisms may underlie the associations of different childhood SEP measures with late life cognitive function.

The conclusion that can be drawn from these studies is that the path from early life SEP to late life cognition is mediated by cognitive development, education and adult SEP. After accounting for these factors, long-term effects of childhood SEP on cognition appear to be minor. In addition, it is likely that in some studies the modest direct effects of childhood SEP on cognition reflect residual effects, stemming from incomplete adjustment for relevant mediators, including cognitive development and subsequent socioeconomic attainment. On the whole, it would appear that the life course socioeconomic trajectory, which is significantly influenced by childhood SEP, is important for cognition in middle and older age.

1.5.2. Education

The relation of education to late life cognitive function and cognitive decline has been the focus of much empirical research. Education was associated with better performance on cognitive tests (15,16,131–137) and reduced risk of dementia (14,138) in numerous studies, but not with slower cognitive decline in longitudinal studies (16,136,137,139,140).

A number of causal and non-causal processes could give rise to the observed association between education and cognition in mid and later life. Not all of these processes are necessarily mutually exclusive, and some may reinforce each other.

The main causal hypothesis suggests that education could benefit cognition directly (141). Education promotes cognitive development by providing mental stimulation and enriched environments and by facilitating acquisition of lasting knowledge relatively early in life (42).

In this way, education could have lasting benefits for cognition by contributing to the formation of cognitive reserve, perhaps by increasing processing efficiency of neuronal networks and facilitating development of compensatory mechanisms. Given that there is little evidence from recent longitudinal studies of education actively slowing cognitive decline, a passive model of cognitive reserve may be appropriate, in which education raises the initial level of cognitive reserve (136).

In contrast, the education-cognition association could also arise from ability-based selection into education (142). Childhood cognitive ability is strongly associated with both subsequent educational attainment and cognitive ability in later life (126,128), and may act as an underlying common cause (142). However, these two processes may be complementary, since education seems to enhance cognition independently of initial cognitive ability (143–145). Notably, recent evidence from one American and two British birth cohorts showed considerable ability-based selection into education, while education also independently enhanced adult fluid cognition (144). In two studies, using instrumental variable design, increases in school leaving age were related to improved cognitive functioning in old age (143,145). In addition, in the 1936 Scottish birth cohort the type of secondary school was associated with cognitive ability at age 70, after employing several controls for selection (146).

Furthermore, cognitive benefits of education may to some extent still be realized in adulthood. In the 1946 British birth cohort, adult education had a small positive effect on cognition, controlling for prior cognitive ability, prior educational attainment and intragenerational social mobility (147). The effect of education on adult cognition, independent of ability-based selection, has been interpreted as both a direct cognitive benefit

(144,145) and an indirect effect, with the competing explanation that educated individuals select environments, occupations and lifestyles conducive to learning and they continue to further stimulate cognition throughout adulthood and later life (146).

It is therefore possible that rather than benefiting cognition directly, the education-cognition association could reflect indirect mechanisms. These include occupation, economic and social resources, and cognitively-engaged, active and healthy lifestyles. Education is positively associated with attainment of higher level occupations, which may, in turn, enhance cognitive performance through greater intellectual demands, mental stimulation and greater complexity of the work environment (148,149). In addition, through its association with occupation and income, education has important economic consequences. However, in the AHEAD study the association between education and late life cognition was not substantially weakened by adjustments for income and wealth, suggesting that material factors may not be the primary mechanism underlying this association (131). Education also provides an easily identifiable credential used by employers to select individuals for particular types of employment with implications for cognitive ageing (42). Furthermore, education shapes non-cognitive skills, such motivation, self-regulation and autonomy, which are associated with economic and personal success in adult life (42,150).

Finally, it has been suggested that the education-cognition association reflects improved test-taking performance in individuals with more education (151). This potential explanation has received less attention. While the explanation is plausible, available evidence suggests that differences in test-taking performance are unlikely to fully explain the education-cognition association (152).

In conclusion, the positive association between education attained early in life and late life cognitive function is a robust finding in epidemiology, although it does not seem to apply to cognitive decline. The mechanisms underlying this association are not yet fully understood, although recent evidence suggests that both social selection and social causation mechanisms are likely to be involved.

1.5.3. Adult SEP

A number of studies have previously reported significant associations between adult SEP, other than education, and cognitive test scores (131,135,153–158), cognitive impairment (159) and dementia (160,161). However, like education, adult SEP measures were not consistently associated with slower cognitive decline in longitudinal studies (16,139).

Multiple pathways could plausibly link adult SEP to midlife and late life cognition. These pathways include the underlying social gradient in health, including life course history of chronic and infectious disease and resulting differences in health status and morbidity, access to medical care, occupational and environmental exposures, economic and social resources, exposure to chronic stress and lifestyle differences in health-related behaviours and participation in cognitively stimulating activities. Some pathways may be more closely related to certain measures of adult SEP than to others, depending on the aspect of adult SEP captured by the respective measure. For example, health and lifestyle may be associated with both income and occupation, and, in turn, cognition, while occupation could also affect cognitive function directly.

Several studies have reported associations between occupation-based SEP measures and better cognitive performance, independently of education (132,156,157,162,163). These studies typically employed occupation as a general indicator of SEP. In contrast, a specific hypothesis suggests that occupation may benefit cognition directly through work complexity and by providing mental stimulation (149,164,165), thus serving as an active component of cognitive reserve (42,166). The "work complexity" hypothesis was directly addressed by several studies, which examined associations between specific occupational characteristics, such as intellectual, physical and social demands, and cognitive performance (148,154,155,165,167,168).

Notably, results from the Wisconsin Longitudinal Study suggest that greater work complexity is associated with better subsequent cognitive performance. At the same time, higher initial cognitive ability was also associated with more complex occupations (148). Similarly, in the Duke Twin Study intellectually demanding work was associated with better late life cognitive performance, independently of education and initial cognitive ability, and the association appeared to be stronger at lower levels of ability (169). However, in two other studies associations between occupational characteristics and improvements in cognition in old age were no longer significant after controlling for midlife cognitive ability (167) or genetic factors (168). Inconsistencies between the results of these studies may in part reflect differences in design, populations and measurement of occupational characteristics. Finally, in addition to work complexity, higher-level occupations may also be associated with longer time spent in active employment and postponement of retirement (42) with possible benefits for cognitive ageing.

Some studies also found higher cognitive test scores to be independently associated with measures of income, wealth or material circumstances (131,135,153,170), although in some of these studies the associations were considerably attenuated after adjusting for education (131). Most of these studies did not include measures of occupation, while Lee et al. (135) found income to be significantly associated with cognition in a cohort with the same occupation. In addition, a longitudinal study of adults in Alameda County, California (171) showed a graded association between sustained economic hardship in adulthood, measured as income below the poverty level, and self-reported memory problems in midlife and early old age. This association appeared to be largely independent of health-based selection into episodes of low income. While this is suggestive of an association between sustained exposure to economic hardship and cognition, it is possible that objective and subjective measures of cognitive performance are differentially related to measures of SEP.

Overall, the association between adult SEP and late life cognition appears to be less robust than for education and dependent on the indicators used to measure adult SEP. However, adult SEP has also been studied less frequently than education, with greater variability in the quality and comparability of measures across studies. This applies to both occupation-based measures and measures such as income and wealth.

1.5.4. Life course SEP

The preceding three sections reviewed studies on midlife or late life cognition with childhood SEP, education and adult SEP as exposures of interest, irrespective of whether they adopted the lifecourse perspective. In this section life course studies of SEP and mid to late life

cognitive function are reviewed. These studies included SEP measures from childhood, adulthood and midlife or old age. Education was typically distinguished from other adult SEP measures and interpreted as a measure of own SEP in young adulthood. A complete summary of life course studies of SEP and cognition is shown in Table 1.1.

In all cross-sectional studies (122,123,172,173) but one (13) SEP measures from all three stages of the life course were independently associated with cognitive function in mid or later life. In these studies associations between childhood SEP and cognition were notably attenuated in the presence of education and adult SEP. The attenuated associations generally remained statistically significant but were mostly of modest strength. In all these studies (122,172,173) the associations between SEP measures from across the life course and cognition were positive and typically graded. In addition, associations of summary scores based on the number of life course stages spent in low/high SEP were also positive and graded, and were interpreted as evidence of a cumulative effect of SEP across the life course on cognition later in life. In contrast, in the Whitehall II study (13) the associations of childhood SEP and education with midlife cognition were fully mediated by adult SEP. However, this study was based on data from an occupational cohort of British civil servants and may not be representative of the general population.

The pattern of life course associations observed in longitudinal studies broadly agrees with the findings from cross-sectional studies but with an important difference of introducing controls for prior cognitive ability. Notably, Richards and Sacker's (126) path analysis of the 1946 British birth cohort showed a strong path from education and a weaker path from adult occupation to midlife cognition, whereas the direct path from father's occupation to cognition was not substantively significant. The association between father's education and midlife

cognition was partially mediated by childhood cognitive ability, and, additionally, by education and occupation. Importantly, in this study the structure of associations was similar for measures of crystallized and fluid ability but the magnitude of the associations was greater for crystallized ability. Similarly, in the 1953 cohort of Danish conscripts (127) father's occupation, education and adult SEP were independently associated with age 57 cognition in ascending order of strength, controlling for adolescent cognitive ability. In contrast, only education was independently associated with age 70 cognitive ability in the 1921 Scottish birth cohort, controlling for childhood cognitive ability (128). Childhood cognitive ability and education also fully mediated the effects of father's occupation and childhood material deprivation on age 70 cognitive ability. Current SEP was not associated with age 70 cognitive ability. However, the measure of current SEP was an index of neighbourhood quality, which may be a less precise indicator of individual-level SEP.

In addition, intergenerational social mobility (upward/downward mobility relative to parental SEP) was examined in three studies (122,172,173). Upwardly mobile individuals had better cognitive function than stable low SEP individuals but not as good as stable high SEP individuals, and vice versa for downwardly mobile individuals. One study (147) examined intra-generational social mobility by considering upward/downward change in own SEP between ages 26 and 53 in the 1946 British birth cohort. This study found a graded positive association between social mobility and midlife cognitive function, adjusting for education and initial cognitive ability. This suggests that the life course social trajectory may be modified by adverse or favourable socioeconomic changes in adulthood.

Overall, life course studies suggest that the association between childhood SEP and cognitive function in mid and later life is mediated by cognitive development, education and adult SEP.

In addition, each of these mediators appears to be independently associated with cognitive function in descending order of strength.

However, several studies on life course SEP and cognition in midlife or older age suggest that the associations between SEP and cognition may be modified by contextual factors. Richards et al. (174) found the structure of life course associations between SEP and adult literacy and numeracy to be relatively stable across two UK birth cohorts but the changing strength of these associations varied in accordance with social structural changes, such as educational expansion, that occurred in the post-war period. Of the three birth cohorts studied by Clouston et al. (144) those with lower adolescent cognition benefited more from education in the U.S. cohort than in the British cohorts, while in the 1946 British cohort women derived a greater cognitive benefit from university education than men but were less likely to attain it. The authors suggested that cognitive and socioeconomic returns to education may be affected by similar forces. Finally, a study of Chinese individuals (175) reported a similar role of social context in shaping the association between childhood SEP and cognition across successive cohorts. These studies suggest that at all stages of the life course the associations between SEP and cognition may be modified by contextual factors.

Most of the aforementioned life course studies come from Western populations. Among studies in non-western settings, two studies in China (175,176) and one study in Latin America (177) showed an association between life course disadvantage and greater odds of cognitive impairment in older age. Thus far no study in non-western settings examined the associations in normal cognitive ageing or included multiple cognitive tests spanning various cognitive domains. Moreover, no studies using data from Central and Eastern European populations were identified.

Table 1.1. Characteristics of included studies on childhood and life course SEP and cognition

Author	Study design	Year	Population	Exposure measurement	Outcome measurement	Covariates	Methods	Findings
Kaplan et al. (2001) (121)	Cross-sectional	Late 1980s	Kuopio Ischaemic Heart Disease Risk Factor Study, males (n=496) aged 58 and 64 years	Parental education and main lifetime parental occupation (as composite index and separately)	Trail Making Test; MMSE; Selective Reminding Test; Verbal Fluency	Education; age; morbidity	Linear regression with complete cases	Childhood SEP index associated with cognition, except verbal fluency. Mother's education directly associated with cognition, father's occupation indirectly but father's education or mother's occupation not associated with cognition.
Everson-Rose et al. (2003) (120)	Cross-sectional		Chicago Health and Aging Project, males and females (n=4,398) aged 65 +	Composite index of parental education, paternal occupational prestige, and self-reported financial status; childhood cognitive milieu	MMSE; East Boston Story (memory); Symbol Digit Modalities test (perceptual speed)	Education	Linear regression	Significant residual associations of childhood SEP and cognitive milieu with cognition, reduced ≥70% adjusting for education.
Lee et al. (2003) (134)	Cross-sectional and longitudinal	1995-2000, follow-up after 2 years	Nurses' Health Study, females (n=19,510), aged 70-79, follow-up (n=15,594)	Father's occupation at age 16; education (categorical, min. 15 years); husband's education (categorical, proxy for adult SEP in cohort with same occupation); household income (census tract-derived quartiles)	TICS; Delayed word recall (10 nouns); East Boston Story; Verbal fluency; Backward digits; Composite global cognition	Age; history of diabetes, high blood pressure, CHD; vitamin E supplements; aspirin use; postmenopausal hormones; BMI; smoking; daily alcohol consumption; antidepressant use; age at menopause; mental health index; vitality index (SF-36)	Logistic regression for low scorers /substantial decliners (bottom 10% of change score distribution); multiple regression for baseline cognitive scores, and mean change with baseline adjustment	*Baseline cognition:* Strongest association with education, weaker for other SEP measures. Lower odds of being low scorer with more education. Weak association with income, none with father's occupation or husband's education. *Cognitive decline:* Lower odds of substantial decline associated with education, but not husband's education or income, and modestly with father's occupation. Similarly for change scores; less decline associated with education, but not husband's education or father's occupation, and modestly with income. Small absolute differences in decline.
Richards & Wadsworth (2004) (129)	Longitudinal		1946 British birth cohort, males and females (n=3,035), aged 53	Material household circumstances	Word recall (15 nouns); letter cancellation; NART (National Adult Reading Test); peg placement task	Sex; parental SEP; birth order, health; education; adult SEP; cognitive ability at ages 8,	Linear regression	Early adversity associated with cognitive ability at ages 8, 15 and 26 and cognition at 43 and 53 years. Long-term effects of early adversity explained by earlier cognitive ability and adult SEP, except for letter

						15 and 26		cancellation.
Life course studies								
Turrell et al. (2002) (173)	Cross-sectional	Late 1980s	Kuopio Ischaemic Heart Disease Risk Factor Study, males (n=496) aged 58 and 64 years	Index of parental education and lifetime occupation; education	Trail Making test; MMSE; Selective Reminding test; verbal fluency	Age	Linear regression	Based on the same cohort as Kaplan et al. (2001). Cumulative SEP scores showed positive and graded association with cognitive function. Social mobility positively associated with cognition.
Richards & Sacker (2003) (126)	Longitudinal		1946 British birth cohort, males and females (n=3,035), aged 53	Father's occupation (Registrar General's); education; occupational social class (Registrar General's);	NART; word recall (15 nouns); letter cancellation	Childhood cognitive ability (reading comprehension, word reading, vocabulary, picture intelligence, 60-item nonverbal reasoning test)	Path analysis with full information maximum likelihood	Indirect association of father's occupation with age 53 cognition. Strong associations of childhood ability and education, and moderate association of adult occupation with age 53 cognition. All associations strongest for NART, weakest for letter cancellation.
Singh-Manoux et al. (2005) (13)	Cross-sectional		Phase 5 of Whitehall II study, males and females, aged 46-68	Parental education, father's social class, and financial problems as latent variable indicators; education; income and occupation as latent variable indicators	Verbal memory, verbal fluency, Mill-Hill, and AH 4-I as latent variable indicators	Age	SEM with full information maximum likelihood	Only indirect association of childhood SEP, small direct association of education, and large direct association of adult SEP with cognition.
Luo & Waite (2005) (122)	Cross-sectional	1998	Health and Retirement Study (HRS), males and females, (n=19,949), aged 50 +	Parental education (<8 years vs ≥ 8 years); father's occupation (white collar vs. other); family financial well-being; education; household income	Telephone Interview for Cognitive Status (TICS); self-reported memory problems	Race; age; sex; childhood health	Linear regression	Significant association of childhood SEP, especially mother's education, with cognition in fully adjusted models. Significant association of education and income with cognition in fully adjusted models. Similar results for self-reported memory problems.
Fritsch et al. (2007) (158)	Longitudinal	2002	Cleveland Longitudinal Ageing Studies of Students, females (58%)	Education (in years); mental, physical and social activities (from high school yearbooks); occupational demands of	TICS; episodic memory (Wechsler); verbal fluency (animals); Timed Backwards Months of the Year (processing	Age 15 IQ; parental occupational class; sex	Path analysis	Direct associations of age 15 IQ and education with cognitive measures. Direct associations of high school mental activities with education and verbal fluency.

			and males, (n=349), mean age 74.8 years	longest-held education	speed)			No association of occupational demands with cognition; explained by education and adolescent IQ. No association of parental occupation with cognition.
Fors et al. (2009) (123)	Cross-sectional	1992, 2002	Swedish Panel Study of Living Conditions of the Oldest Old (SWEOLD), males and females, aged 77+	Father's occupational class; economic hardship; number of siblings; parental absence; family conflict; education; social class	Shortened MMSE	Period; sex; age group	Logistic regression	Direct association of childhood SEP (father's manual class vs non-manual, family conflict) with cognition reduced adjusting for education, and social class. Significant associations of higher education and being manual worker with cognition.
Johnson et al. (2010) (128)	Longitudinal		1936 Lothian birth cohort, males and females, aged 70	Father's occupational social class and education; childhood deprivation; education (years); Registrar General's social class; neighbourhood environmental quality (age 70)	IQ (age 70)	Age; sex; IQ (age 11)	Path analysis with full information maximum likelihood	Strong association of age 11 IQ and weaker of education with age 70 IQ. Father's occupation and childhood deprivation associated with age 11 IQ, negative effect of father's education. Neighbourhood quality not associated with age 70 IQ.
Haan et al. (2011) (172)	Cross-sectional	1998-1999	Mexican Americans, males and females (n=1,789), aged 60-100	Composite index of parental education, occupation, food deprivation, sibling mortality (all binary); composite index of education, occupation and income (all binary); cross-classified childhood and adult SEP summary scores	3MSE; Spanish English verbal learning test (SEVLT)	Age; sex; heath status	Mixed linear models	Childhood SEP significantly associated with cognition but slight adjusting for adult SEP. Social mobility positively associated with cognition. Cumulative disadvantage moderately associated with cognition.
Jefferson et al. (2011) (130)	Cross-sectional	2002-2008	Rush Memory and Ageing Project, Chicago metropolitan area, females (74%) and	Parental education (in years); paternal occupation; no. of children, community-level SEP in childhood; education (coded 0-30), occupation; income (age	Global cognition; episodic memory (WMS-R Logical memory, East Boston story, word list learning); Semantic memory (Boston Naming Test; verbal fluency);	NART (premorbid IQ) ; age; sex; race	Path analysis	Education strongly associated with cognition (but not with perceptual speed, and second to NART for working memory). Cognitive activities, especially early life, strongly associated with perceptual speed. Adult SEP not associated with

			males (n=951), aged 79 ± 8	40 & baseline); cognitive activities (CAS questionnaire for early, mid and late life)	working memory (WMS-R digit span, Digit ordering); visuo-spatial ability (Line orientation 15-items, Raven's progressive matrices); perceptual speed (Symbol digits Modalities test, Number comparison, Stroop colour-word interference)			cognition. Significant total effect of childhood SEP, stronger than for adult SEP.
Osler et al. (2012) (127)	Longitudinal	2009-2011	Metropolit cohort, Copenhagen, Denmark, males (n=11,532) born in 1953	Father's occupation at birth (self-employed or salaried, skilled worker, unskilled worker and unknown) ; leisure activities at age 12 (questionnaire, no. of intellectual, physical and social activities); education at age 18 (basic to high school); occupational social class (5 social classes, cross-classified by the no. of subordinates, classes I and II high overlap with university education)	Age 12: Harnquist test battery (incl. geometric figures, number series, verbal analogies); Age 18: BBP (incl. geometric figures, number series, verbal analogies, letter matrices); Age 57: Sentence completion, verbal analogies, number series from Intelligenz Struktur Test	Mother's age; mother's material status at birth; birthweight	Linear regression	Correlations between age 57 cognition and cognition at ages 12 and 18 were 0.67 and 0.70, respectively. Cognitive ability at age 57 weakly associated with father's occupation, own education, strongly with adolescent cognitive ability and significantly with adult social class in fully adjusted models. Association of father's occupation with age 57 cognition considerably weakened adjusting for education, adolescent cognition, and adult SEP.
Low and middle income countries								
Zhang et al. (2008) (176)	Cross-sectional and longitudinal	1998; follow-up 2000	Chinese Longitudinal Healthy Longevity Survey, males and females (n=8,444), aged 80-105	Urban residence (yes/no); went to bed hungry (yes vs no); education (some schooling vs none)	Chinese adaptation of MMSE, CI ≤ 18	Age; sex; lifetime occupation (professional/ admin vs other)	Logistic & multinomial regression	Urban residence and education associated with lower odds of baseline cognitive impairment (CI). Weak association of childhood advantage with lower odds of CI onset during 2-year follow-up, especially in women.

Historically, Central and Eastern Europe had smaller income inequalities than other countries at similar or higher levels of development and studies in Central and Eastern European populations may add a broader dimension to existing research on life course associations between SEP and cognition. In the second half of the 20th century Communist regimes tried to minimize material inequalities between different social groups, and this resulted in relatively weak correlations between education or occupation and income. This and other aspects of social stratification in Central and Eastern Europe under Communism were discussed in detail in Section 1.4. If the distinct socialist social stratification pattern can be assumed to have been consequential for life course accumulation of risk, then this may be reflected in the structure of life course associations between SEP and cognition of middle-aged and older individuals in these populations. Consequently, an investigation of life course associations between SEP and cognitive function in mid and later life in four Central and Eastern European populations constitutes one of major aims of this thesis.

In concluding this section, it is worth reiterating that beyond any direct effects of SEP on cognition, the plausible pathways linking SEP to mid-late life cognitive function include the underlying social gradient in health, which may be partly driven by differences in health-related behaviours. In Section 1.4. alcohol consumption and smoking have been identified as significant factors contributing to the high cardiovascular disease burden and premature mortality in the region. At the same time, both childhood and adult socioeconomic circumstances are important determinants of CVD risk (178), and, in turn, cardiovascular risk factors are likely to be important for cognitive ageing (179). Since alcohol consumption and smoking behaviour tend to be socially patterned, it is anticipated that in these four Central and Eastern European populations both alcohol consumption and smoking may be important mediators of the associations between life course SEP and mid-late life cognitive function as

well as likely independent risk factors for cognitive function. The latter is the subject of the next section.

1.6. Core health behaviours and cognitive function

Health behaviours are important risk factors for many health outcomes, and inverse associations between SEP and health behaviours are well established. Indeed, health behaviours have been identified as plausible mediators of the associations between SEP and various health outcomes, including cardiovascular (180) and all-cause mortality (181), and may also mediate the associations between SEP and mid to late life cognitive function. In addition, health behaviours appear to be independently associated with cognitive function in mid and later life (11,154,182), possibly by affecting cognitive ageing through their associations with cardiovascular risk factors (179).

This section reviews empirical research and theoretical perspectives on mid to late life cognitive function and its relationship to two core health behaviours, alcohol consumption and smoking, and is accordingly divided into two parts. The first part examines empirical research on alcohol consumption and cognitive function, and discusses the current knowledge on plausible mechanisms underlying this association. Despite a multitude of observational studies in this area several important gaps in empirical literature on alcohol and cognitive function are identified, and subsequently addressed in this thesis. The second part reviews

empirical research on smoking behaviour and mid to late life cognitive function and examines plausible mechanisms for this association.

1.6.1. Alcohol consumption

The relation between light-to-moderate drinking and cognition in middle and older age has been the focus of much recent attention. Before proceeding, it should be noted that there is no accepted definition of light-to-moderate drinking and considerable variation in what is taken to constitute light-to-moderate drinking, or indeed a drink, is observed across studies, and this may partly reflect lack of consensus in international guidelines on what constitutes moderate drinking levels or a standard drink (183). A meta-analysis of prospective studies on alcohol and cognitive outcomes noted that operational definitions of light-to-moderate drinking typically ranged between 1–14 drinks to 2–28 drinks per week across studies (17). While this suggests significant overlap in definitions of light-to-moderate drinking between studies, the range is still considerable. A recent consensus paper (184) suggested that consuming no more than 30 g of ethanol per day for men and 15 g per day for women constitutes moderate or safe drinking, based on reviewing evidence on the associations between alcohol and a number of health outcomes, including dementia and cognitive impairment, but despite such attempts a standard definition of moderate drinking levels appears elusive.

Despite significant variation in operational definitions of light-to-moderate drinking, observational studies generally show it to be positively associated with cognitive outcomes in mid and later life, compared to non-drinking, or report no difference. Two recent meta-analyses (17,185) concluded that longitudinal evidence on light-to-moderate drinking is

suggestive of reduced dementia risk. The most comprehensive meta-analysis (186) to date, which defined moderate drinking to be social, non-alcoholic drinking and used consuming more than 3-4 drinks per day as a cut-off for heavy drinking, found moderate drinking to be associated with reduced risk of all types of dementia and cognitive impairment but not cognitive decline. In addition, these authors also reviewed 52 recent studies examining the relationship between moderate drinking and cognitive test scores in older participants, of which just over a half reported better cognitive performance in drinkers compared to non-drinkers and the rest reported no difference. Thus, on the whole, observational evidence is indicative of a positive association between moderate alcohol consumption and cognitive performance in mid and later life. Characteristics and an update of recent meta-analyses and systematic reviews on alcohol consumption and cognitive function are presented in Table 1.2. and Table 1.3., respectively.

Whereas moderate alcohol consumption may be cognitively protective and, based on current observational evidence, certainly does not appear to reduce cognitive performance in older age, it is not clear whether this also extends to heavy drinking. Chronic heavy alcohol use is known to cause neurocognitive impairment in adults of all ages, and alcohol-related disorders, such as Wernicke-Korsakoff syndrome and alcohol-related dementia, are widely recognized (187). However, findings from population studies in middle-aged and elderly adults on the association between high alcohol consumption and cognitive function have been inconsistent.

Several cross-sectional (188–190) and longitudinal studies (191–194) found a J- or an inverted U-shaped relationship between alcohol consumption and cognitive function, indicating that cognitive function is better among moderate drinkers compared to abstainers

and heavy or excessive drinkers. However, in some of these studies the association between heavy drinking and worse cognitive performance was not statistically significant. Moreover, several studies reported better cognitive function across categories of drinkers (195–197) or found worse cognitive function among heavy drinkers but only in specific subgroups such as individuals with low socioeconomic position (198). In several studies the association varied by gender (192,196,199–201). Finally, in some studies the associations in heavy drinkers were domain-specific (195,196,201,202) but current evidence is not sufficient to say whether some cognitive domains are more sensitive to the effects of heavy alcohol consumption than others.

In addition, two meta-analyses of moderate drinking also reported results for higher-than moderate intake. Anstey et al. (17) found no increase in dementia risk among heavy or excessive drinkers, compared to non-drinkers. This finding was based on four studies and pooled associations in heavy drinkers vs. non-drinkers, which showed slightly reduced, increased and borderline increased risk of Alzheimer's disease, vascular dementia and any dementia, respectively, but were not statistically significant. Neafsey and Collins (186) included a much broader range of studies and found high alcohol consumption (>3-4 drinks/day) to be associated with non-significantly higher cognitive risk, compared to non-drinkers.

In sum, the findings on heavy drinking and cognitive function in middle and older age are based on relatively few studies with generally few participants in the high alcohol consumption group. The relatively low numbers of heavy drinkers in these studies may indicate a lower chance of being selected for the study among heavier drinkers because of sampling or survival effects (17) and this may have contributed to insignificant and

inconsistent results. In addition, in most of these studies cognitive performance in heavy drinkers was not the primary interest.

Drinking pattern may have an independent effect on cognitive function or modify the association between alcohol volume and cognition. However, surprisingly few studies of alcohol and cognition have considered drinking pattern. An episodic pattern of drinking (in binges), with alcohol consumption concentrated in a single occasion or over a few drinking days leading to intoxication and followed by withdrawal, is thought to confer a higher health risk than a comparable total intake based on regular but moderate consumption. Only two reports with relatively small sample sizes, based on only one cohort of Finnish twins, examined binge drinking and found both binge drinking and alcohol-induced blackouts at midlife to be independently associated with increased risk of cognitive impairment (203) and dementia (204) in older age. This important finding requires confirmation in other populations and settings, before it can be considered robust. In addition, associations between drinking pattern, including binge drinking, and cognitive test scores, which reflect normal cognitive ageing, and not just specific neurodegenerative conditions such as dementia, have not yet been examined.

The role of alcohol consumption in cognitive health is of particular interest in Central and Eastern Europe, where alcohol intake is generally high (205) and premature mortality attributable to alcohol is estimated to be higher than in the rest of Europe (20). Moreover, high rates of binge drinking are characteristic of parts of the region, especially Russia and neighbouring countries (205). According to the recent WHO global status report on alcohol, which assigns risk scores to countries based on drinking behaviour and alcohol-attributable disease burden, Russia has a high-risk drinking pattern (206). In comparison, Lithuania, the

Czech Republic and Poland were estimated to be medium risk. Since average per capita alcohol consumption in Russia is not unusually high, - WHO estimate for Russia was similar, lower, and higher to that for Lithuania, the Czech Republic and Poland, respectively (206) - this further points to the potential importance of drinking pattern in modifying the associations between alcohol consumption and health outcomes.

The causal nature of the association between alcohol consumption and cognition continues to be debated. A J- or an inverted U-shaped relationship whereby moderate alcohol consumption is associated with better health than heavy drinking and abstention has been reported for many health outcomes, including all-cause mortality (207) and cardiovascular disease (208,209). Cardiovascular health is one of the plausible mechanisms underlying the association between alcohol consumption and cognitive function in mid and later life. Epidemiological studies have linked cognitive performance to cardiovascular disease, peripheral arterial disease, and specific vascular risk factors, including cholesterol, hypertension and fibrinogen levels (210–214). The J- or inverted U-shaped association between alcohol consumption and cardiovascular health is consistent with both cardioprotective and adverse effects of alcohol on vascular function, and this relationship appears to be conditional on volume and drinking pattern (215).

In observational studies light-to-moderate drinking has been linked to improved vascular profiles, including lower platelet aggregation, lower fibrinogen levels, increased fibrinolytic activity, favourable lipid profiles, such as higher levels of high-density lipoproteins, and decreased ischemia-reperfusion injury (216). In addition, moderate drinking may reduce inflammation from atherosclerotic plaques, and act favourably on insulin resistance (215).

Although cardioprotective effects associated with alcohol consumption may be the result of alcohol itself, it has been suggested that polyphenolic antioxidants, especially resveratrol, may be primarily responsible. Wine, and red wine in particular, has high resveratrol content, although resveratrol is also found in smaller concentrations in other alcoholic drinks, such as beer. Some studies have suggested that wine consumption may reduce vascular risk to a greater extent than consumption of beer (217) or spirits (218). A meta-analysis concluded that wine drinking may be associated with better cognitive function relative to drinking beer and spirits (186), and lower vascular risk in wine drinkers could explain this association. However, other studies found no difference in cardiovascular risk reduction by type of alcohol (219,220), and the finding of better cognitive outcomes in wine drinkers was based on only a small number of studies. In addition, the hypothesized mechanisms of alcohol-mediated cardioprotection are similar for both alcohol and resveratrol, calling the usefulness of this distinction into question (216). However, neuroprotective action mechanisms of resveratrol have been described, suggesting that resveratrol may also have direct effects on the brain (221,222). Thus, wine drinking could, indeed, be associated with better cognitive performance, compared to drinking other types of alcohol.

In contrast to light and moderate drinking, heavy drinking is thought to increase cardiovascular risk. Heavy drinking has been linked to increased blood clotting, reduced threshold for ventricular fibrillation, increased low-density lipoproteins, no increase in high-density lipoproteins, and increased risk of thrombosis after cessation of drinking (215). High or excessive alcohol consumption may predispose to histological changes in the myocardium and vascular system (215), and raises the risk of ischemic stroke as well as haemorrhagic and total stroke (223). In addition, irregular heavy drinking has been linked to increased risk of sudden cardiac death (224), particularly in studies based on Eastern European populations

(72,225–227). However, a recent meta-analysis on irregular heavy drinking occasions and risk of ischemic heart disease concluded that despite its plausibility, the evidence for the association with sudden cardiac death has been mostly indirect and requires further research (228). Finally, the association between binge drinking and increased cardiovascular mortality has been shown to be independent of total alcohol volume (215).

In addition to being mediated by cardiovascular health, effects of alcohol on cognitive function via direct effects on the brain are also plausible. Moderate alcohol consumption has been shown to facilitate anti-inflammatory processes in the brain (216) and protect the brain against ischemia through preconditioning phenomena in neurons (229). Conversely, chronic alcohol exposure can lead to structural and functional brain damage, and is associated with brain atrophy (230), and particularly loss of white matter (231). Moreover, repeated withdrawal, characteristic of binge drinking pattern, may be associated with greater neuronal damage (187). Finally, negative effects of heavy drinking could result from direct neurotoxic effects of ethanol or, alternatively, alcohol-related nutritional deficiency (232).

Despite the plausibility of cardiovascular and direct cognitive pathways, possible non-causal explanations of the alcohol-cognition association should also be given due consideration. Notably, moderate drinking may be a reflection of a moderate lifestyle characterized by relatively healthy behaviours, which may partly explain the link with cognitive function. In addition, socioeconomic position and initial cognitive ability (233) have been shown to be associated with alcohol consumption, and may provide a complete or partial explanation of the association between (moderate) alcohol consumption and mid and late life cognitive function (233,234). For example, in a Scottish birth cohort the positive association between total alcohol intake and age 70 cognition was significantly attenuated after adjusting for

childhood cognitive ability and adult socioeconomic position (233). However, significant associations were still observed between total alcohol intake or consumption by type of alcohol and some cognitive functions. Previously, a study in a sample of older British adults found no association between moderate drinking and cognition after adjusting for premorbid intelligence and physical functioning (234).

Another potential issue with causality is related to behaviour change as a result of poor health, such as poor cognitive status or cognitive decline. These issues are inherent in the "former drinkers problem" (235). Epidemiological studies typically compare drinkers with non-drinkers but are often unable to distinguish between lifelong abstainers and former drinkers and, additionally, drinkers, who substantially reduced their alcohol consumption from previously high levels. Non-drinkers may be an inappropriate comparison group because they may include individuals who quit drinking because of poor health (the so-called "sick quitter" hypothesis (236)) or have a history of past problem drinking. Thus, the apparently protective effect of moderate alcohol consumption on cognition might be attenuated or lost, if the former drinker bias was adequately addressed in observational studies. For example, some of the apparently protective effect of moderate alcohol consumption on cardiovascular risk appears to be partly attributable to the non-drinker bias (237). These issues are ameliorated but not eliminated by using infrequent or light drinkers instead of non-drinkers as the comparison group (235). Furthermore, other lifestyle, dietary and social factors may differ between non-drinkers and drinkers.

Notably, a recent Mendelian randomization study based on data from HAPIEE, Whitehall II and ELSA (unpublished), using ADH1B genotypes as instrumental variables, found no association between alcohol consumption and cognitive function, a result inconsistent with a

causal interpretation. In addition, an earlier Mendelian randomization study (238) in Chinese individuals, using ALDH2 genotypes as instrumental variables, also found no association between moderate alcohol consumption and cognitive function, further suggesting that the association between low-to-moderate alcohol consumption and cognitive function may be largely driven by selection, social factors and lifestyle. Interestingly, in another Mendelian randomization study in the same Chinese cohort moderate alcohol consumption was not associated with fasting glucose, self-reported CVD and IHD, and was actually associated with higher diastolic blood pressure and HDL-cholesterol, suggesting only a weak link with cardiovascular disease in this cohort. However, these studies examined only occasional and moderate drinkers and did not consider heavy drinking or a potential modifying role of drinking pattern.

In view of identified gaps in the literature, the particular focus of this thesis will be on investigating the associations between heavy drinking and drinking patterns, including binge drinking and preference for type of alcohol (wine, beer or spirits), and mid-late life cognitive function in four Central and Eastern European populations. In addition, potential biases introduced by misclassification of former drinkers and drinkers who reduced their alcohol consumption will be explored in one population with relevant data (Novosibirsk).

Table 1.2. Characteristics of included meta-analyses and systematic reviews on alcohol and cognitive outcomes

Author	Inclusion criteria	Studies	Pooled association	Conclusions
Meta-analyses				
Anstey et al. (2009) (17)	Prospective studies, with primary outcomes incident dementia or cognitive decline.	15 prospective studies, with follow-ups ranging from 2-8 years, and samples including 14,646 participants for Alzheimer disease, 10,225 for vascular dementia, and 11,875 for any dementia. 4 studies for analysis of heavy vs. non-drinkers for Alzheimer disease, and any dementia, and 3 studies for vascular dementia.	Pooled relative risks (RRs) of AD, VaD, and any dementia for light to moderate drinkers vs. non-drinkers were 0.72 (95% CI = 0.61-0.86), 0.75 (95% CI = 0.57-0.98), and 0.74 (95% CI = 0.61-0.91), respectively. Drinkers vs. non-drinkers had a reduced risk of AD (RR = 0.66, 95% CI = 0.47-0.94) and any dementia (RR = 0.53, 95% CI = 0.53-0.82) but not cognitive decline. Heavy drinkers vs. non-drinkers had RR=0.92 [0.59-1.45] for AD, RR=1.36 [0.68-2.71] for vascular dementia, and RR=1.04 [0.69-1.56] for any dementia.	Alcohol drinking vs. non-drinking in late life was associated with reduced dementia risk. Heavy drinkers did not have an increased dementia risk compared with non-drinkers, possibly due to sampling bias. Not clear whether the association between moderate drinking and reduced dementia risk reflects selection effects in cohort studies starting in late life, a protective effect of alcohol consumption throughout adulthood, or a specific benefit of alcohol in late life.
Neafsey & Collins (2011) (186)	Broad inclusion criteria, all study types (longitudinal and cross-sectional) considering alcohol and dementia, AD, cognition, mild cognitive impairment (MCI), cognitive decline, or memory	143 papers, of two types: 1.) 74 papers with risk ratios between drinkers and non-drinkers, and 2.) 69 papers (52 recent) with cognitive function in drinkers rated as "better," "no different," or "worse" than cognition in non-drinkers	Low-to-moderate alcohol consumption protective or no relationship For ratio studies average risk ratio for dementia or CI/cognitive decline in moderate drinkers was 0.77, compared to non-drinkers. Reduced risk was found for all dementia types (dementia unspecified, AD, and vascular dementia) and CI (low test scores), but not cognitive decline (rate of decline in test scores).	Moderate drinking either reduced or had no effect on dementia or CI risk in post-1998 studies with test scores. Light and moderate drinking provided a similar benefit, but heavy drinking was associated with non-significantly higher risk of dementia and CI. Wine was better than beer or spirits, but this was based on few studies, some of which found no difference. Presence of APOE epsilon 4 allele eliminated the benefit of moderate drinking but this was based on few studies, of which some found epsilon 4 allele to be protective. Moderate drinking was beneficial in both genders, despite differences in amount and pattern of drinking. Association was seen in 14/19 countries with country-specific ratio data, and 3/5 remaining countries showed non-significant reductions. Concluded that light to moderate drinking does not impair cognition in younger subjects and reduces dementia and CI risk in older subjects.
Peters et al. (2008) (185)	Longitudinal studies of subjects aged 65, with primary outcomes incident dementia or cognitive decline.	23 studies (20 cohort studies, 3 retrospective matched case-control studies nested in a cohort)	Positive association between low alcohol consumption and lower risk of dementia (random effects model, RR 0.63; 95% CI 0.53-0.75), and Alzheimer's disease (RR 0.57; 0.440-0.74). No association for vascular dementia (RR 0.82; 0.50-1.35), and cognitive decline (RR 0.89; 0.67-1.17)	Significant heterogeneity found in the data (differing follow-up lengths, measurement of alcohol intake, definition of abstainers, selection of confounders), complicating interpretation of findings. Some evidence to suggest that low alcohol intake in earlier adult life is associated with lower dementia incidence.

Systematic reviews				
Panza et al. (2012) (229)	Evaluated English literature published on alcohol and dementia or predemntia syndromes before September 2011	14 cross-sectional and 20 longitudinal studies with subjects aged 55+ years	Light-to-moderate alcohol consumption may be associated with a reduced risk of incident overall dementia and AD. Associations of light-to-moderate drinking with vascular dementia, cognitive decline, and pre-dementia syndromes are less clear.	Latest of several reviews by these authors. Concluded that protection of moderate alcohol consumption from cognitive decline is more likely in absence of APOE epsilon 4 allele, and if wine is consumed. No indication that light-to-moderate alcohol drinking is harmful to cognition or raises dementia risk. Based on current evidence not possible to define a level of alcohol intake beneficial for cognitive performance. Cross-sectional designs, restrictions by age or gender, or incomplete ascertainment identified as possible reasons for inconsistent findings. Different outcomes, alcohol types, drinking patterns, study follow-up periods and possible interactions with other lifestyle-related (e.g. smoking) or genetic factors (e.g. APOE gene variation) identified as contributing to variability of findings.

Table 1.3. Recent epidemiological studies of alcohol and cognition in middle-aged and older populations (update of meta-analyses and systematic reviews)

Author	Study design	Year	Population	Exposure measurement	Outcome measurement	Covariates	Methods	Findings
Yeung et al. (2010) (239)	Cross-sectional	2003-2008	Guangzhou Biobank Cohort Study, males and females, aged 50+ (delayed recall, n= 28,537); (MMSE, n=9,571)	Alcohol categories: never, occasional (<1 per week), moderate (20 g/30 g per day for women/ men), heavy, and former drinker.	Delayed recall (10 nouns); MMSE	Age; sex; education; physical activity; smoking; systolic & diastolic blood pressure; tri-glycerides; LDL-cholesterol, blood glucose; BMI; waist/hip ratio	Multiple linear regression	Occasional drinkers and moderate male drinkers had better cognitive performance.
Yeung et al. (2010) (238)	Cross-sectional	2003-2008	Guangzhou Biobank Cohort Study, males only, aged 50+, (delayed recall, n =4,707; MMSE, n= 2,284)	Alcohol units (10 g ethanol per day)	Delayed recall (10 nouns); MMSE	Aldehyde dehydrogenase 2 (*ALDH2*) genotype (AA, GA, or GG) used as instrumental variable	2-stage least squares regression	Contrary to observational design (see above), alcohol consumption was not associated with cognitive performance in Mendelian randomization design.
Corley et al. (2011) (233)	Longitudinal	2004-2007	Lothian birth cohort 1936, males and females (n=922), aged 70	Alcohol at baseline from FFQ, calculated overall total intake and by type of alcohol (wine/beer/spirits) in UK units; categorized into non-drinkers, ≤2 units daily, and >2 units daily for descriptive purposes only	PCA derived g factor; processing speed factor; memory factor; verbal ability; MMSE; House-Moray test	Martial status; eduction; smoking medical history; BMI; physical activity; RG's adult social class; age 11 IQ (House Moray test)	General linear models	Alcohol intake showed a weak indepdendent association with memory and verbal ability. Childhood cognitive ability and socioeconomic status partly explained the association between alcohol intake and improved cognition.
Gross et al. (2011) (202)	Longitudinal	1947-2005	Johns Hopkins Precursors Study, (n=588) 72 years at cogntive assessment	Alcohol quantity-frequency measures at multiple occasions from age 55; CAGE	TICS; semantic and phonemic fluency; verbal word list–learning test; the Brief Test of Attention (BTA)	Age; sex; hypertension; smoking status	Generalized estimating equations	Weekly quantity and frequency of alcohol at midlife were associated with lower phonemic fluency. No associations with other measures of cognitive function. Phonemic fluency was significantly better among those who drank 3-4 drinks per week compared to daily or almost daily drinkers. Global cognition was not associated with alcohol intake at any point over follow-up. No

								association bteween cogntive function and CAGE.
Lyu & Lee (2012) (201)	Cross-sectional	2004	Health and Retirement Study (HRS), females (n=3,888) and males (n=2,350)	Non-drinker ("do you ever drink?" at basline), non–excessive drinker, excessive drinker (i.e. ≥ 1 days a week ≥ 3 drinks for males, and ≥ 2 drinks for females or CAGE ≥ 2)	Immediate word recall (10 nouns); delayed recall (10 nouns); serial 7s; TICS	Age; race; marital status; education; income; smoking; exercise; self-rated health; depression; IADLs; medical history; vision; hearing; BMI	Linear regression; logistic regression	In fully adjusted models non-drinkers vs. non-excessive drinkers in women had lower fuild cogntion scores and lower TICS scores, fuild cognition of male non-drinkers and excessive drinkers in both sexes was not significantly different from non-excessive drinkers but female excessive drinkers had significantly higher likelihood of having lower TICS scores.
Kesse-Guyot et al. (2012) (188)	Longitudinal	1994–1996 2007-2009	SU.VI.MAX (1994), French middle-aged adults (n=3,088)	Alcohol intake from 24-h dietary records every 2 months for a total of 6 records per year	Delayed cued recall test; semantic and phonemic fluency; forward and backward digit span; the Delis-Kaplan trail-making test	Sex; age; smoking status, medication use; occupational category; retirement status; physical activity; education; anthropometric measurements; blood pressure	ANCOVA	Lower cogntive scores in female abstainers In men, heavy drinkers (>3 drinks/day) had higher cognitive scores than did low-to-moderate. Lower composite cognitive score was detected in male drinkers consuming ≥90 g/d (≈8 drinks/d). Drinking beer was associated with lower cognitive scores.
Zanjani et al. (2013) (197)	Longitudinal	1998-2005	Seattle Longitudinal Study, males and females, aged 45+ yrs (n=571)	Alcohol drinking status (abstainer, moderate drinker [<7 drinks/pw], and at-risk drinker [>8 drinks/pw]), derived from questions on quantity of beer, wine and spirits consumed in past week	6 standardized cognitive domain scores , based on 29 cognitive tests, modelled as latent variables (memory, reasoning, spatial, verbal number, and speed abilities)	Age group; education; smoking; income at baseline	Linear mixed models	Abstainers, and to a lesser extent, moderate drinkers showed declines in verbal ability, while at-risk drinkers were stable. Relationship between alcohol and decline in verbal ability was linear. Association between decline in spatial ability and alcohol status was modified by age, and in women decline in perceptual speed was greater in abstainers vs. drinkers.

1.6.2. Smoking

Smoking is a known risk factor for many health outcomes and premature mortality (240), and is also a possible risk factor for cognitive impairment and decline (11). Results of epidemiological studies have not been entirely consistent but generally indicate that smoking is associated with increased risk for negative cognitive outcomes in middle-aged and older adults. In a Dutch cohort of men and women current smokers showed worse baseline performance on tests of global cognition, mental speed and cognitive flexibility, and accelerated decline in global cognition, flexibility and memory over a 5-year period (241). Similarly, in a large multi-cohort study current smoking was associated with faster decline on the MMSE, and higher number of pack years of smoking was associated with greater rate of decline (242). In a study of British civil servants faster cognitive decline in global cognition and executive function was observed in male but not female current smokers and recent ex-smokers, compared to never smokers and long-term ex-smokers (243).

A systematic review and meta-analysis (244) of studies in adults aged 65 and over found an increased risk of AD and a non-significantly increased risk of vascular dementia, any dementia and cognitive decline in current smokers, whereas the relationship in former smokers was ambiguous. Previously, a meta-analysis of longitudinal studies (18) found an increased risk of vascular dementia, any dementia, AD and cognitive decline in current smokers, and, for the latter two outcomes, also in former smokers, compared to never smokers.

Initial cognitive ability and socioeconomic position may confound of the effect of smoking on cognitive function in middle and older age. In the 1936 Scottish birth cohort current

smoking remained associated with lower general cognitive ability and processing speed at age 70 after controlling for childhood cognitive ability and adult SEP (245), confirming previous findings from the 1921 Scottish birth cohort (246). In the 1946 British birth cohort, smoking was associated with faster decline in verbal memory and slower mental speed at baseline, and these associations were independent of gender, socioeconomic position, adolescent cognitive ability and health status, but were largely accounted for by individuals who smoked more than 20 cigarettes per day (247). In contrast, an early study in middle-aged men found lower cognitive test scores in current smokers, compared to never and former smokers, but no cognitive performance gradient in association with total lifetime tobacco consumption, suggesting there had been prior selection of smokers, and especially, men who later gave up smoking (248). However, subsequent studies found a dose-response association between increasing number of pack years of smoking and faster decline on several cognitive tests (241–243).

It has been suggested that differences in cognition associated with smoking may be underestimated in epidemiological studies because of selective non-participation or drop-out and increased mortality in smokers. Sabia et al. (243) estimated that smoking status differences in cognitive decline in the Whitehall II study would have been as much as 1.5 times greater accounting for selective attrition.

Potential mechanisms for the harmful effect of smoking include increased risk of cardiovascular and cerebrovascular diseases, oxidative stress in the brain and other organs and increased inflammation. Richards et al. (247) noted that the failure of cardiovascular and other health factors in explaining the association between smoking and cognition in their study suggests that smoking may act directly on the brain. Many constituents of tobacco

smoke have known neurotoxicity as well as toxic effects on cardiovascular and pulmonary systems (249). In contrast, plausible beneficial effects of nicotine on cognitive function have also been described. Nicotine binds to nicotinic acetylcholine receptors in the brain, increasing the levels of several neurotransmitters, and has been linked, at least in the short-term, with improved attention, reaction time, and some aspects of learning and memory.

Smoking is a likely confounder of the association between alcohol and cognitive function, and both exposures could plausibly modify each other's relationship with cognitive function (229). In a recent study of British civil servants heavy drinkers, who were also current smokers, showed accelerated cognitive decline over a 10-year period (250). However, the evidence for interaction between heavy drinking and smoking in this study was weak and requires confirmation in other settings.

In summary, compared to never smokers, and possibly former smokers, current smokers generally, but not always, showed worse performance and faster declines in several cognitive domains in most epidemiological studies, and, to some extent, this could plausibly result from direct harmful effects of smoking on cognitive function. Since they are associated with SEP, both smoking and alcohol consumption are also strong candidates for mediating the associations between SEP and cognition as well as being independently associated with cognitive function in mid and later life.

Chapter 2. Aims and objectives

Building upon the gaps in existing research identified in Chapter 1, this chapter outlines the aims and objectives of this thesis. This work has three major aims, each of which is subdivided into several smaller objectives. The first part of this chapter outlines the aims and objectives relating to SEP and mid to late life cognitive function, followed by an outline of aims and objectives relating to two core health behaviours, alcohol consumption and smoking, in the second part.

Part 1: Life course SEP

The literature review on SEP and mid to late life cognitive function revealed generally significant associations of education and adult SEP with cognitive function. In addition, generally modest or non-significant independent associations between childhood socioeconomic factors and cognitive function in later life, which were significantly mediated by later SEP, point to the importance of life course socioeconomic trajectory for subsequent cognitive function. These studies were largely conducted in Western settings, while studies in Central and Eastern European populations are currently lacking. Central and Eastern European populations with historically smaller income inequalities and a distinct social stratification system would help clarify to what extent the observed pattern of associations

and the pathways underlying it are universal rather than context-specific. This leads to the first major aim:

Aim 1: To investigate the associations between SEP measures from across the life course and cognitive function in middle-aged and older persons in four Central and Eastern European populations.

This aim requires the following specific objectives to be fulfilled:

Objective 1.1: To investigate the direct effects of life course SEP on cognitive function in these Central and Eastern European populations.

Objective 1.2: To investigate the indirect and total effects of childhood SEP and education on cognitive function in these Central and Eastern European populations.

Objective 1.3: To investigate associations between SEP measures from the different stages of the life course in these Central and Eastern European populations.

One plausible pathway linking SEP to mid-late life cognitive function is the underlying social gradient in health, which may be partly explained by differences in health-related behaviours. Given that alcohol consumption and smoking are typically socially patterned, both behaviours may be significant mediators of the associations between life course SEP and mid-late life cognitive function in Central and Eastern European populations.

Objective 1.4: To investigate whether the associations between SEP measures from the different stages of the life course and cognitive function in these Central and Eastern European populations are significantly mediated by alcohol consumption and smoking.

Independent effects of SEP measures relating to childhood, young adulthood and mid to later life in relation to cognitive function in mid and later life will be estimated in preliminary regression analyses. In preliminary regression analyses age-adjusted and mutually adjusted associations between SEP measures from across the life course and cognitive function will be estimated. The models will then be adjusted for alcohol consumption and smoking to investigate whether these two core health behaviours significantly mediate the associations between SEP and cognitive function. Finally, the models will be further adjusted for health measures (selected mediators and confounders).

In order to comprehensively address the above objectives, a structural equation model will then be specified, explicitly relating SEP measures from the different stages of the life course to each other, and to cognitive function in mid and later life. In this way, direct as well as indirect and total effects of childhood SEP and education on cognitive function will be estimated, and the role of life course social trajectory evaluated. In addition, by modelling the associations between SEP measures the importance of childhood SEP for subsequent educational and socioeconomic attainment in these formerly communist populations will be revealed. The model will be estimated for both domain-specific and global measures of cognitive function as outcomes.

Part 2: Core health behaviours

It is anticipated that both alcohol consumption and smoking may be important mediators of the associations between SEP and cognitive function as well as independent predictors of mid to late life cognitive function in Central and Eastern European populations. Accordingly, Aim 1 includes an objective (Objective 1.4.) pertaining to the role of alcohol consumption and smoking as potential mediators of the associations between SEP and cognitive function, whereas the focus of Aims 2 and 3 and their associated objectives will be on the investigation of independent associations between these two core health behaviours and mid-late life cognitive function in four Central and Eastern European populations.

Alcohol

The literature review overwhelmingly suggested that light-to-moderate alcohol consumption is related to better cognitive performance in midlife and older age, compared to non-drinking, although the causal nature of this association remains disputed. In addition, wine appeared to be associated with better cognitive function than spirits or beer but this is based on relatively few studies and any definite conclusions would be premature. In contrast to the large number of studies and several meta-analyses on moderate drinking and mid to late life cognitive function, few studies examined the association in heavier drinkers and with conflicting results. In addition, even fewer studies investigated the potential role of drinking pattern in modifying the associations between alcohol consumption and cognitive function. Only two studies from one cohort were identified, which examined independent effects of binge

drinking on a late life cognitive outcome. Notably, studies of alcohol consumption and cognitive function are largely lacking in Central and Eastern European populations. Heavy drinking and binge drinking are relatively common in Central and Eastern Europe, and alcohol consumption has been linked to the high cardiovascular disease burden and premature mortality in the region. As a result, the second major aim of this thesis is:

Aim 2: To investigate the associations between mid and late life alcohol consumption and mid and late life cognitive function in four Central and Eastern European populations.

This aim has the following specific objectives:

Objective 2.1: To investigate the associations between conventional measures of alcohol consumption, including quantity and frequency measures of alcohol consumption, and cognitive function in these four populations, with special focus on heavy drinking.

Objective 2.2: To investigate the associations between drinking pattern and cognitive function in these four populations.

Objective 2.3: To investigate whether binge drinking is independently associated with cognitive function, after accounting for total alcohol consumption.

Objective 2.4: To investigate whether type of alcohol is associated with cognitive function in these four populations.

Conventional measures of alcohol consumption, including quantity and frequency, as well as the potential modifying role of drinking pattern and binge drinking will be explored. In addition, associations between alcohol consumption and cognitive function will be adjusted for selected mediators and relevant confounders. Some studies found better cognitive performance in wine drinkers relative to beer and spirit drinkers. In this thesis the associations between preferred type of alcohol and mid to late life cognitive function in populations, in which beer and spirit drinking predominates, will be explored. The associations will be estimated for both domain-specific and global measures of cognitive function as outcomes.

Finally, it has been suggested that the positive association between light-to-moderate alcohol consumption and better cognitive outcomes, compared to non-drinking, may be explained by misclassification of former drinkers who quit drinking because of poor health, among non-drinkers. Similarly, the association between alcohol and cognitive function may be biased by misclassification of current drinkers, who significantly reduced their previous alcohol consumption because of poor health or problems related to drinking, among stable low-risk drinkers. The relationship between mid and late life cognitive performance and past drinking behaviour, including reasons for quitting drinking in former drinkers, will be explored in the Novosibirsk sample, where relevant data on past drinking was collected.

Objective 2.5: To investigate whether past drinking behaviour biases the association between current alcohol consumption and cognitive function in Novosibirsk, and whether the difference in cognitive performance between drinkers and non-drinkers is biased by the inclusion of former drinkers with poor health among current non-drinkers.

Smoking

Finally, the literature review suggested that smoking was associated with worse cognitive performance and faster cognitive decline in several domains. However, conclusions with regard to smoking history were less consistent, with several studies failing to find a dose-response effect on cognition. No studies of smoking and cognitive function were identified in Central and Eastern European populations. Rates of smoking are very high among men in Central and Eastern Europe, and during the transition smoking rates have also increased in women. Smoking is one of the key factors responsible for the high premature mortality in the region. Smoking is also associated with greater risk of cardiovascular disease, and may thus be a significant risk factor for cognitive functioning in these populations. With this in mind, the third and final major aim of this thesis is:

Aim 3: To investigate the associations between smoking behaviour and cognitive function in middle-aged and older persons in four Central and Eastern European populations.

This aim has the following specific objectives:

Objective 3.1: To investigate the associations between current smoking status and cognitive function in middle-aged and older persons in four Central and Eastern European populations.

Objective 3.2: To investigate the associations between smoking history (pack years of smoking) and cognitive function in middle-aged and older persons in four Central and Eastern European populations.

Objective 3.3: To investigate whether the associations between smoking status and cognitive function are modified by the level of alcohol consumption by testing for interactions between smoking and alcohol.

In addressing these objectives, the investigation of smoking behaviour in relation to cognitive function will account for selected mediators and relevant confounders. The associations will be estimated for both domain-specific and global measures of cognitive function as outcomes.

Chapter 3. Methodology

This chapter outlines the methodology employed in this work. The chapter opens with a description of methodological aspects which are of general relevance to all analyses, including study populations and participants, response rates, measurement of outcome variables, exposure variables and covariates, and missing data. Statistical analysis plan is described in Section 3.6., which is divided into three parts, detailing analyses of cognitive function with life course SEP, alcohol consumption and smoking as exposures of interest, respectively.

3.1. Study population

The HAPIEE (**H**ealth, **A**lcohol and **P**sychosocial factors **I**n **E**astern **E**urope) study is one of the largest prospective epidemiological multi-centre studies of middle-aged and older persons ever conducted in Central and Eastern Europe. It was originally established to study determinants of cardiovascular and other non-communicable diseases in Central and Eastern Europe, and its focus was subsequently extended to include healthy ageing. Details the study protocol have previously been published by Peasey et al. (251). In brief, between 2002 and 2005 random population samples of 28,945 men and women aged 45-69 years were recruited in Krakow (Poland), Novosibirsk (Russia) and six Czech towns (Hradec Kralove, Jihlava, Karvina, Kromeriz, Liberec and Usti nad Labem) from population registers and electoral lists

(Novosibirsk). In each centre the samples were stratified by gender and five year age groups, so that an equal number of persons in each age group were invited to participate. Participant numbers and response rates are shown in Table 3.1.

Table 3.1. Participant numbers and response rates in the HAPIEE study

	Baseline 2002-2005/ 2006-2008‡	Response rate (%)	Wave 2 2006-2008	Response rate (%)
Czech towns	8,857	59%	5,343	60%
Novosibirsk	9,360	61%	6,182	66%
Krakow	10,728	61%	6,629	62%
Kaunas	7,164	65%	-	-
Total	**36,109**	**62%**	**18,154**	**63%**

‡ Date for Kaunas baseline.

Data were collected by structured questionnaires and clinical examination. The questionnaire consisted of detailed sections on health (including complete medical history), health-related behaviours, past and current socioeconomic circumstances, food frequency, psychosocial factors and psychosocial environment at work. In addition, working participants completed a special module on work characteristics, and retired participants completed a brief module on retirement and quality of life. A generic version of the questionnaire was in English. All questions were translated from English into each language, and then back translated to ensure consistency and accuracy. In Novosibirsk, both the questionnaire and the examination were completed in a clinic. In Krakow and Czech towns, participants were visited at home to complete a structured questionnaire, and then invited to a clinic for a short examination. Therefore, not all participants in these centres, who completed the health questionnaire, also attended the clinical examination and have data on both questionnaire and examination; the proportion of participants with full data is 82% in Czech towns and 87% in Krakow (251).

The short examination included measurement of cognitive function, height, weight, blood pressure, lung function, trunk length, waist and hip circumference, and a fasting venous blood sample. Data entry of baseline questionnaires and medical examination data in Czech towns and Novosibirsk was done using Epi-Info 6 software, and questionnaires were electronically scanned in Krakow.

Re-examination of the three cohorts was conducted between 2006 and 2008. At that time a fourth cohort, consisting of a random sample of 7,164 men and women aged 45-72 years recruited from a population register in Kaunas (Lithuania), joined the study. The average follow-up response rate in Czech towns, Novosibirsk and Krakow was 63%. Baseline response rate in Kaunas was 65%. The majority of questions and measures from the baseline health survey were repeated at follow-up with some new sections added to the structured questionnaire. In Kaunas these data were collected simultaneously. Re-examination interviews and baseline interviews in Kaunas were conducted using face-to-face Computer Assisted Personal Interview (CAPI).

The study was approved by the ethics committee at University College London and University College Hospital, UK and by the local ethics committee in each participating centre. Written informed consent was obtained from all participants.

The study populations are considered to be broadly representative of urban populations in their respective countries. Novosibirsk is the capital and major industrial centre of western Siberia, and with just under

1.5 million inhabitants the third largest city in Russian Federation. Despite its Siberian location, available data suggest that Novosibirsk is fairly typical of urban population in Russian Federation in terms of social development (252), lifestyle (253) and mortality trends (254). Two city districts with different social profiles were selected for the study. Krakow is an industrial centre of South-west Poland, and with a population of about 1.3 million the second largest Polish city. Although Krakow is more prosperous than the Polish average, the four city districts selected for the study range from a predominantly blue-collar district to a middle-class district in the city centre. The six Czech towns, with a total population of about 600,000, are of varied social profiles, ranging from a former mining town (Karvina), which had one of the highest unemployment rates in the country at the time of the study, to a prosperous town (Hradec Kralove) with service and trade-oriented economy and low unemployment. Finally, Kaunas city is an industrial, trade and service centre and the second largest Lithuanian city with a population of over 340,000.

3.2. Response rates

As discussed by Peasey at al. (251) achieving adequate response rates was an important consideration of the study and the final response rates are similar to contemporary studies in the region and elsewhere. While relatively high response rates were typical of surveys conducted in Central and Eastern Europe before 1990, response rates have since declined rapidly. This may partly reflect the more general trend of declining response rates to epidemiological studies observed in recent years (255). In this study the actual response rates are believed to be higher than those reported for two reasons. First, a non-negligible

proportion of non-respondents had moved away or died before the start of the study and were therefore not eligible to participate. Based on extrapolation from the proportion of incorrect addresses identified in home visits in Novosibirsk and Krakow, and from assessment of the accuracy of the population register in one Czech town, it was estimated that actual response rates correspond to ≥68% in Krakow, ≥71% in Novosibirsk and >60% in Czech towns. Second, a further proportion of non-respondents could not be contacted after three home visits, and many may not live at their officially registered address, suggesting that the actual response rates are likely to be even higher.

As part of the study, a small survey was conducted in a subsample of non-responders. The survey suggested that non-participation rates were higher in men, decreased with age, increased with low educational level and poorer self-rated health, and were higher among smokers. This conforms to the general observation that participants in epidemiological studies tend to be wealthier and healthier than those who refuse participation, and that participation rates are generally higher among women and lower among persons with unhealthy behaviours (255).

3.3. Measurement

This section describes measurement of outcome and exposure variables as well as substantive and methodological covariates used throughout this thesis.

3.3.1. Cognitive outcomes

At baseline in Czech towns, Novosibirsk and Krakow cognitive function was assessed in all retired participants and a random 20% of working participants. Different characteristics, relating to either retirement or employment, were assessed in retired and working participants but, for comparability, cognitive function was also assessed in a subsample of working persons. At follow-up in Czech towns, Novosibirsk and Krakow and Kaunas baseline, cognitive function was assessed in all participants regardless of retirement status. The same cognitive tests were administered across centres and survey waves. Cognitive tests were administered by trained staff and conducted as part of a clinic-based examination in Czech towns, Novosibirsk and Kaunas, and home-based assessment in Krakow. Participant numbers for each cognitive assessment are shown in Table 3.2.

Table 3.2. Number of participants with cognitive data in the HAPIEE study

	Czech towns	Novosibirsk	Krakow	Kaunas	Total
Total number examined					
Survey baseline	3,679	4,751	4,295	7,051	19,776
Wave 2	5,258	6,040	6,497	-	17,795
Analytic sample					
Baseline measure	6,500	7,590	8,242	7,051	29,383
Repeated measures	2,437	3,205	2,551	-	8,193

From 35,956 participants, who completed the baseline health questionnaire, 29,383 (81.7%; 73.8% in Czech towns, 81.3% in Novosibirsk, 76.8% in Krakow, and 99.5% in Kaunas) participated in at least one cognitive assessment. In addition, 67.3% (n= 9,607) of participants in the three original cohorts had repeated measurements of cognitive function.

Flowchart showing selection of analytic sample for cognitive function used in this thesis is shown in Figure 3.2. The analytic sample is based on baseline cognitive data for all participants; in Czech towns, Novosibirsk and Krakow, where some participants had repeated measurements of cognitive function, the first measurement was used. By using the baseline at first cognitive measurement for all participants the results are not affected by practice effects in participants with repeated measurements, and the number of participants with cognitive data is significantly increased by also including participants, whose first cognitive assessment was at follow-up in the three original cohorts.

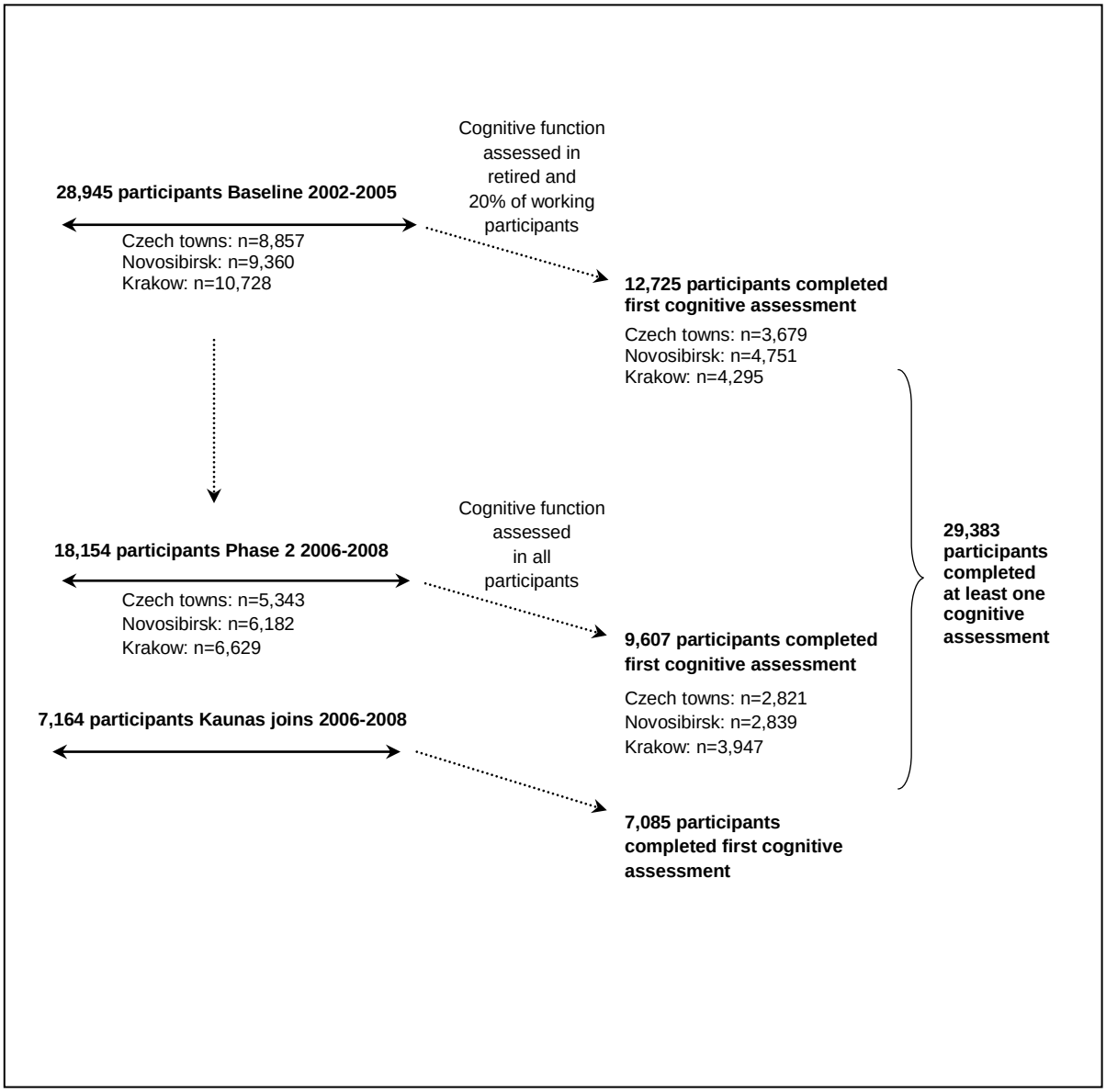

Figure 3.1. Flowchart showing selection of analytic sample for cognitive function

Cognitive assessment consisted of four tests of fluid cognition as summarized in Table 3.3. The tests were adapted from Consortium to Establish a Registry for Alzheimer's disease (CERAD) test battery (256) and cognitive test battery used by the English Longitudinal Study of Ageing (ELSA) (257). The tests were chosen because they are sensitive to ageing and morbidity and because they measure cognitive functions, which are instrumental for coping with the demands of daily living.

Table 3.3. Description of cognitive tests available in the HAPIEE study

Cognitive test	Outcome	Description	Cognitive domains
Word recall (immediate)	Total correct (min=0; max=30)	Recall of 10 common 2-syllable nouns in 1 minute over 3 consecutive trails	Verbal memory and word learning
Verbal fluency	Total correct (min=0)	Animal naming (name as many different animals within 1 minute)	Executive function
Letter cancellation	Total correct (min=0; max=65)	Also known as letter search, letter search speed or visual search speed test. Cross-out P and W (Р and Ш in Russia) randomly embedded in an A4 grid consisting of 780 other random letters arranged in rows and columns in 1 minute .	Mental speed and concentration
Delayed recall	Total correct (min=0; max=10)	Recall of 10 nouns following an interval	Learning ability
Derived			
Global cognition	Average of above four tests	Averaged centre and sex-specific z-scores (mean=0; SD=1) from individual cognitive tests (immediate recall, delayed recall, verbal fluency and letter cancelation)	Global (fluid) cognition

The four tests were as follows: First, learning ability was assessed using a word list of 10 common 2-syllable nouns. The word lists were the same in each centre. Participants were played a tape recording (digital recording in CAPI) of the words at the rate of one word every 2 seconds, and then given 1 minute to recall the words. The procedure was repeated three times. The correct responses from these three immediate consecutive recall trials were summed to give an overall score (range 0-30). The calculations were based on participants, who had data for all three recall trials. Second, delayed recall was assessed by recall of the 10 nouns after an approximately five minute interval, during which other cognitive tests were administered. The total number of correctly recalled words (range 0-10) was used as the outcome measure in analysis. Third, verbal fluency was assessed by asking participants to name as many animals as possible in 1 minute. Names of different species counted towards the total but redundancies did not. The total number of correctly named animals was used. Finally, mental speed and concentration was assessed by a letter cancellation task. Participants were instructed to cross out two target letters, P and W, randomly embedded in an A4 grid of other random letters arranged in rows and columns as quickly and as accurately as possible within 1 minute. In Russia, where Cyrillic alphabet is used, Р and Ш, were chosen

because they are visually similar to the Latin characters. Measurement instruments used at cognitive assessment are shown in Appendix I.

Z-scores rather than raw scores on each test were used as outcome measures in regression analyses throughout the thesis to ensure comparability across centres. In addition, a global cognitive score was created using the four tests by first standardizing the raw scores on each individual test to z-scores (mean=0; SD=1) using centre and sex-specific means and standard deviations for each test. The z-scores were then averaged to obtain a global cognitive score, which is thought to minimize the amount of measurement error.

3.3.2. Exposure variables

Exposure variables used in this thesis include measures of life course SEP, alcohol consumption and smoking behaviour, described in corresponding sections below and summarized in Table 3.6.

3.3.2.1. Life course SEP measures

1.) Childhood SEP

Childhood SEP was assessed using self-reported measures of parental education and the number of basic amenities participants had access to when they were approximately 10 years old.

For the purpose of the thesis highest educational level attained by both parents was categorized into: less than primary (incomplete primary or no formal education), primary, secondary and university (degree). To ensure comparability across centres, vocational and general secondary educational levels were collapsed into a single category for secondary education, combining original categories for vocational education (apprenticeship), secondary education and college (Kaunas only). In the Czech sample data on parental education was collected at follow-up rather than at baseline. Consequently, Czech participants who were lost to follow-up had missing values for parental education. In all remaining centres parental education measures were self-reported by participants at baseline.

At survey baseline, participants recalled whether their household had access to the following basic amenities when they were approximately 10 years old: cold tap water, hot tap water, radio, fridge, own kitchen and own toilet. Possible responses were: “yes”, “no”, and “I don't remember”. Very few participants chose the latter (<2% per item per centre on 91% of occasions) and ‘don't remembers’ were thus treated as negative responses. Responses were then summed to give a total score (range 0 to 6). Internal consistency of the childhood basic amenities scale was assessed using Cronbach’s alpha, and was 0.73 for the pooled sample. While generally adequate, reliability of the scale was lower in Kaunas than in the other centres as shown in Table 3.4.

Table 3.4. Scale reliability for childhood amenities

	Czech towns	Novosibirsk	Krakow	Kaunas	All centres
Cronbach’s alpha					
Household amenities in childhood	0.67	0.73	0.78	0.55	0.73

2.) Education

At baseline participants were asked about the highest level of education they had completed, and could choose between the following categories: incomplete primary or no formal education, primary, vocational (apprenticeship), secondary, college (Kaunas only), and university (degree). At Kaunas baseline expanded response categories distinguishing between various vocational (e.g. vocational with incomplete secondary, vocational with complete secondary) and technical streams (e.g. technical college) of secondary education were introduced halfway through the study. In addition, education data with expanded response categories was collected in a sub-sample of Novosibirsk participants at follow-up.

Comparison of responses in a subset of Novosibirsk participants using the original and expanded response category scales suggested that agreement between expanded vocational categories and the two original categories (vocational (apprenticeship) and secondary education) was relatively low, with participants with various vocational qualifications self-classifying as having completed either vocational or secondary education. In addition, vocational education may also not have the same meaning across all centres.

To ensure comparability across centres categories for vocational and secondary education and college in Kaunas were collapsed into a single category for secondary education in all centres. In addition, very few participants (n=237 (0.7%) pooled sample) had incomplete primary or no formal education and were thus grouped together with participants with complete primary education. For the purpose of the thesis the final categorization of participants' highest level of education, reported at baseline, was: primary or less, secondary and university.

In addition, at follow-up in Czech towns, Novosibirsk and Krakow and at baseline in Kaunas participants were also asked about the age at which they completed full-time education, and this measure was used to confirm whether the majority of participants completed formal schooling in or before young adulthood, as assumed in this thesis.

3.) Adult SEP

The main measure of adult SEP was the number of durable household assets (car, mobile phone, colour TV, satellite/cable TV, video recorder, video camera, fridge, microwave, dishwasher, washing machine and landline) owned at cognitive assessment. Ownership of each asset was recorded on a three-point scale: "yes", "no, I do not want it", and "no, I cannot afford it". The latter two answers were combined, and responses were then summed to give a total number of household assets owned (range 0 to 11). These eleven assets were chosen from a longer list of assets to ensure consistency of the measure across centres and survey waves. Internal consistency of the asset scale (Cronbach's alpha=0.71 for pooled sample) was adequate. In addition, scale reliability did not vary significantly across centres, as seen in Table 3.5.

Table 3.5. Scale reliability for household assets

	Czech towns	Novosibirsk	Krakow	Kaunas	All centres
Cronbach's alpha					
Household assets in adulthood	0.70	0.71	0.71	0.70	0.71

In addition, a measure of economic hardship at cognitive assessment was used in preliminary analyses. It was measured by three questions asking participants how often they did not have enough money for: 1) food, 2) clothes, and 3) to pay the bills. Responses were evaluated on a

five-point scale, ranging from “never” (scored 0) to “most of the time” (scored 4). Responses to the three questions were then summed to give a total score (possible range 0-36), with higher scores corresponding to greater hardship. Cronbach’s alpha for the economic hardship scale was 0.75 for the sample as a whole (range from 0.86 in Krakow to 0.70 in Kaunas).

3.3.2.2. Alcohol consumption indices

At both survey waves alcohol consumption in the past year was evaluated by interview using the graduated frequency questionnaire (GFQ). In those Czech, Novosibirsk and Krakow participants, whose first cognitive measurement was at follow-up, corresponding measures of alcohol consumption from follow-up were used. At baseline in Czech towns, Novosibirsk and Krakow, the GFQ consisted of nine mutually exclusive categories of frequency (ranging from “never” to “daily/almost daily”) and six mutually exclusive categories of amounts of alcohol consumed per occasion, expressed in local units (0.5 l of beer, 0.2 l of wine and 0.05 l of spirits), ranging from between half a drink and ten drinks or more (the questionnaire is shown in Appendix II, on pg. 248).

Shortened versions of the GFQ were used at follow-up in Czech towns, Novosibirsk and Krakow, and Kaunas baseline. The GFQ used at follow-up consisted of three mutually exclusive categories of amounts consumed per occasion, ranging from between half a drink and two drinks to five drinks or more, whereas the GFQ used at Kaunas baseline consisted of four categories of amounts, ranging from between half a drink to five drinks or more. The same nine mutually exclusive categories of frequency were used in both versions. One drink was standardized as containing 20 g of ethanol.

In order to determine alcohol consumption in the year preceding cognitive assessment for each participant included in the analytic sample, the data were harmonised across centres and survey waves using the follow-up GFQ as the standard (as seen in Appendix II, on pg. 248). There was high agreement between the original and harmonised data, and in participants with repeated measures harmonised alcohol consumption indices at baseline and alcohol consumption indices at follow-up were also highly correlated.

Several indices of alcohol consumption at cognitive assessment were subsequently derived from the harmonised GFQ data. First, total alcohol intake in the past year was converted into average daily consumption in grams of ethanol, and categorized into four groups: non-drinkers (0 g per day), light drinkers (≤5/10 g per day in women/men), moderate drinkers (5-20/10-40 g per day in women/men) and heavy drinkers (≥20/40 g per day in women/men). Second, drinking frequency, calculated as the number of drinking occasions in the past year, was grouped into five categories: never, less than once a month, 1-3 times a month, 1-4 times a week and every day or almost every day. Third, average quantity consumed per occasion in grams of ethanol (dosage) was calculated by dividing the total alcohol intake in the past year by the total number of drinking occasions, and categorized into: <25 g, 25-40 g, 40-60/80 g in women/men, and >60/80 g per occasion in women/men. Fourth, drinking pattern was categorized into five groups combining information on drinking frequency and quantity of alcohol consumed per single occasion: non-drinkers, occasional moderate (≤2/4 drinks per occasion less than weekly for women/men), regular moderate (≤2/4 drinks per occasion at least weekly for women/men), occasional heavy (≥2/4 drinks per occasion less than weekly for women/men) and regular heavy (≥2/4 drinks per occasion at least weekly for women/men) drinkers. Fifth, binge drinking was defined as consuming 60 or 100 g of ethanol or more in a single occasion at least once a month for women and men, respectively.

When categorizing alcohol indices, lower cut-off values were used for women than men because gender differences in alcohol consumption patterns are known to be large (258) and women in these cohorts have very low levels of alcohol consumption.

Finally, separate questions on self-reported total intake of beer, wine and spirits in a typical week, included at baseline in all four centres and repeated at follow-up, were used to assess consumption by type of alcohol. Participants were classified as beer, spirit or wine drinkers, if the given alcohol type constituted 75% or more of their total weekly consumption.

In addition, at Novosibirsk baseline participants were also asked about their past drinking behaviour, and to give reasons for changing their drinking behaviour had they reported doing so. Participants were asked whether they used to drink more alcohol than they had during the past year, and their responses were coded as a binary variable (yes vs. no). Participants, who responded affirmatively, were also asked to give reasons for the change in drinking behaviour, and could give health-related or other reasons. The question on past drinking behaviour was repeated at Novosibirsk follow-up (binary; yes vs. no), and used to update the information for those participants, whose first cognitive measurement was at follow-up. At Novosibirsk follow-up only participants, who gave up drinking, were asked whether they had given up drinking because of health-related or other reasons. On the basis of this information, several categories of past drinking behaviour were distinguished: stable non-drinker (current non-drinker, reported never drinking more), former drinker (current non-drinker, reported drinking more in the past), stable drinker (current drinker, did not report drinking more in the past) and reduced use drinker (current drinker, reported drinking more in the past). In addition, former drinkers were classified into those, who stopped drinking because of health-related reasons vs. other reasons. This measure was available for 6,281 out of 6,962

Novosibirsk participants with cognitive function data. Finally, past drinking behaviour was also cross-classified with current alcohol intake and drinking frequency to distinguish current levels of alcohol consumption among stable and reduced use drinkers.

3.3.2.3. Smoking measures

Data on current smoking status and smoking history were collected during baseline interview and repeated at follow-up. In those Czech, Novosibirsk and Krakow participants, whose first cognitive measurement was at follow-up, corresponding measures of smoking status and smoking history were used.

Smoking status at cognitive assessment was categorized into: never smoker, current smoker and former smoker (smoked in the past but stopped). Participants were categorized as current smokers, if they reported regularly smoking either less than one cigarette a day or at least one cigarette a day. A relatively low number of participants reported regularly smoking less than one cigarette a day (n=533). A small number of participants (n=359) with first cognitive measurement at follow-up reported conflicting combinations of smoking status between baseline and follow-up (e.g. current smoker at baseline, never smoker at follow-up or former smoker at baseline, never smoker at follow-up). Most of these participants were former smokers at baseline with complete and meaningful information on age started and stopped smoking, and were reclassified as former smokers accordingly. The rest (n=108) were excluded from the analyses.

The interview also included questions on age at which participants started smoking (baseline questionnaire only), age at quitting smoking (for former smokers, both waves) and the average number of cigarettes smoked per day (both waves). This was used to calculate pack years at cognitive assessment as the average number of cigarettes smoked per day, divided by the number of cigarettes in a typical pack (20), times years as a smoker for ever smokers. For Czech, Novosibirsk and Krakow participants, whose first cognitive measurement was at follow-up, pack years of smoking inclusive of the period between baseline and follow-up were calculated. Pack years of smoking could be calculated for 12,213 (94.7%) of 12,893 ever smokers with complete data on all variables required for the calculation. The number of pack years measures lifelong exposure to cigarettes, whereas smoking status measures smoking behaviour at a single point in time.

Table 3.6. Complete list of exposure variables used in main statistical analyses

Measure	Description	Type	Coding	Measurement wave
Life course SEP				
Childhood SEP				
Basic amenities at age 10	Number of basic amenities participant's household had access at age 10 (cold tap water, hot tap water, radio, fridge, kitchen and toilet)	Continuous	Summated scale, range 0-6	Baseline
Mother's education	Highest completed educational level of mother	Categorical/ continuous	Less than primary, primary, secondary, university	Baseline (Czech towns: Wave 2)
Father's education	Highest completed educational level of father	Categorical/ continuous	Less than primary, primary, secondary, university	Baseline (Czech towns: Wave 2)
Adult SEP				
Education	Highest completed educational level	Categorical	Primary, secondary, university	Baseline
Mid-later life SEP				
Household assets	Number of durable household assets owned, based on answers to: "Do you have [asset] in your household?" (car, mobile phone, colour TV, satellite/cable TV, video recorder, video camera, fridge, microwave, dishwasher, washing machine, landline)	Continuous	Summated scale, range 0-11	Baseline/ Wave 2

Table 3.6. continued

Health behaviours				
Alcohol consumption				
Total alcohol intake	Total alcohol consumption in past year	Categorical/ Continuous	Non-drinker, light, moderate, heavy drinker	Baseline/ Wave 2
Drinking frequency	Frequency of drinking in past year	Categorical	Never, less than once a month, 1-3 times monthly, 1-4 times a week, daily/ almost daily	Baseline/ Wave 2
Binge drinking	≥ 60 or 100 g of ethanol in a single occasion at least once monthly in women and men, respectively	Binary	Yes vs. no	Baseline/ Wave 2
Quantity per occasion	Total alcohol intake in the past year divided by the total number of drinking occasions	Categorical	Non-drinker, ≤25 g, 26-40 g, 41-60/80 g, >60/80 g	Baseline/ Wave 2
Drinking pattern	Drinking frequency cross-classified by quantity of alcohol consumed per single occasion	Categorical	Non-drinker, occasional moderate, regular moderate, occasional heavy, regular heavy drinker	Baseline/ Wave 2
Wine drinker	Wine makes up ≥75% of typical weekly alcohol consumption	Binary	Wine vs. other alcohol	Baseline/ Wave 2
Beer drinker	Beer makes up ≥75% of typical weekly alcohol consumption	Binary	Beer vs. other alcohol	Baseline/ Wave 2
Spirit drinker	Spirits make up ≥75% of typical weekly alcohol consumption	Binary	Spirits vs. other alcohol	Baseline/ Wave 2
Past drinker	"Did you stop drinking/used to drink more in the past?"	Binary	Yes vs. no	Novosibirsk only Baseline/ Wave 2
Reason stopped/reduced drinking	"Why did you stop/reduce your drinking?"	Binary	Health-related reason vs. other reason	Novosibirsk only Baseline/ Wave 2
Smoking behaviour				
Smoking status	Do you smoke cigarettes?	Categorical	Current, former, never smoker	Baseline/ Wave 2
Pack years	No. of cigarettes smoked daily times years as smoker divided by 20	Continuous/ categorical	Centre-specific quintiles, if categorical	Baseline/ Wave 2

3.3.3. Covariates

Covariates used in the thesis were selected based on substantive knowledge from previous studies. The analyses were adjusted for potential confounders, and the associations were generally also evaluated after including selected potential mediators. Additionally, exposures of interest in a given set of analyses may have acted as confounders or mediators in another set of analyses. Depending on exposure of interest, substantive covariates could include measures of socioeconomic position, age, health behaviours and health measures. Where

there was prior research suggesting potential interactions between exposure variables and covariates, the possible presence of effect modification was also examined. Measurement of covariates is described below and a summary of covariates is given in Table 3.7.

Socio-demographic measures

1.) Age

Age at cognitive assessment was measured in integer years, and ranged from 45-78 years. It was categorized into 5- or 10-year age groups, when used to conduct additional analyses stratified by age. In was included as a confounder in all inferential statistical analyses.

2.) SEP measures

Participants' education and household asset ownership at cognitive assessment were included as potential confounders in analyses of cognitive function with alcohol and smoking as exposures of interest.

Health behaviours

1.) Alcohol intake & smoking status

Total alcohol intake (as categorical variable) was included as a potential confounder in analyses of smoking and cognitive function. Current smoking status was included as a potential confounder in analyses of alcohol consumption and cognitive function. Both

measures were included as hypothesized mediators in preliminary regression analyses of life course SEP and cognitive function.

Health measures

1.) Self-rated health

Across centres and survey waves participants rated their health over the last 12 months on a 5-point scale as: “very good”, “good”, “average”, “poor” or “very poor”. Self-rated health at cognitive assessment was measured as a continuous variable, with higher scores indicating better health (range 1-5). Self-rated health, as a measure of overall health, was included as a potential confounder in analyses of cognitive function with alcohol and smoking as exposures of interest. Self-rated health was also included in preliminary regression analyses of cognitive function and life course SEP, although in this case it could also act as a mediator, for example, between childhood SEP or education and cognitive function.

2.) Self-reported medical history

Medical history was assessed by a list of specific chronic conditions. At both survey waves participants were asked about past physician diagnosis or hospitalisation for myocardial infarction (MI), angina or ischemic heart disease (IHD) and stroke, and presence of high blood pressure and diabetes. All variables were binary (no vs. yes), and scored 0/1. All medical history variables were included as covariates in analyses of cognitive function with alcohol and smoking as exposures of interest, and preliminary regression analyses of cognitive function and life course SEP.

Additional substantive covariates

Statistical models used in this thesis could be extended in a number of ways. However, with the main socioeconomic variables, health behaviours and health measures already included, it seemed unlikely that adding additional socioeconomic and health covariates would significantly improve explanatory power of the models. Therefore, the final statistical models were parsimonious in that they included only covariates which were found to be substantively important and/or were statistically significant, and for which comparable measures were available across centres for all participants with cognitive data. Nevertheless, supplementary analyses were carried out with some additional health and lifestyle covariates, which were of substantive interest but for which comparable measures were unfortunately not available across centres for all participants with cognitive data.

Physical activity and the presence of depressive symptoms were used as covariates in supplementary analyses because the available measures were not directly comparable across centres and survey waves. In order to examine whether the results were likely to be significantly affected by inclusion of physical activity and the presence of depressive symptoms, albeit with imperfect measures, analyses were repeated with the available measures of physical activity and depressive symptoms. In addition, measures of cardiovascular risk factors from the baseline clinical examination were also used as covariates in additional analyses. The measures included: BMI, systolic and diastolic blood pressure, resting pulse, and low- and high-density lipoproteins. Measurement of physical activity, depressive symptoms and vascular risk factors from the baseline clinical examination is described below.

Health behaviours

1.) Physical activity

At baseline participants reported the number of hours in a typical week spent on leisure-time physical activity, such as sports, walking, and hiking. At follow-up and in Kaunas the number of hours in a week typically spent on leisure-time physical activity in summer and winter was reported. For participants whose first cognitive assessment was at follow-up, the average of the two values was used. Correlations between baseline and follow-up measures of physical activity in the three original centres were not particularly high. Because of differences in methodology across centres and waves, leisure-time physical activity in a typical week was coded as a binary variable (none vs. some). Physical activity was included as a potential confounder in supplementary analyses of cognitive function with alcohol consumption and smoking as respective exposures. The measure was also included as a potential mediator in supplementary regression analyses of life course SEP and cognitive function.

Health measures

1.) Depressive symptoms

Depressive symptoms at cognitive assessment were measured using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D 20) (259) at baseline in Czech towns, Novosibirsk and Krakow, and the 10-item version at follow-up and Kaunas baseline. In Czech towns, Novosibirsk and Krakow the frequency of experiencing 20 depressive symptoms during the past week was evaluated on a four-point scale: never, less than 1 day, 1-2, and 3-4 days. The 10-items, corresponding to the short version of the scale, were used and

responses were scored 0-3 and summed to give a total score (range 0-30). Participants scoring 11 or higher were classified as having depressive symptoms. At follow-up and Kaunas baseline the presence of 10 depressive symptoms during the past week was evaluated on a two-point scale: yes (1) or no (0), and summed to give a total score (range 0-10). Kaunas participants and participants with first cognitive measurement from follow-up scoring 4 or higher were classified as having high depressive symptoms. Presence of depressive symptoms was included as a potential confounder in supplementary analyses of cognitive function with life course SEP, alcohol consumption and smoking as respective exposures.

2.) Baseline clinical examination measures

Blood pressure and resting pulse were measured three times, with a two minute interval between measurements, using an Omron M5-I digital blood pressure monitor, after a five-minute rest. Systolic and diastolic blood pressure values averaged over the three measurement occasions were used as continuous variables in regression analyses. Weight and height were measured at clinical examination, and used to calculate body mass index (BMI) as weight (kg) divided by height (metres) squared. Biochemical analyses of fasting blood samples were conducted, and lipid concentrations were analysed locally. High density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol concentrations in serum were determined using a conventional enzymatic method.

These measures were available only at study baseline. Current measures of cardiovascular risk factors were thus not available for participants in Czech towns, Novosibirsk and Krakow, whose first cognitive measurement was at follow-up. Baseline measures of cardiovascular risk factors were used for these participants but this might have resulted in a significant number of participants being misclassified. In order to examine whether the findings might be

explained by the inclusion of objectively-measured cardiovascular risk factors, albeit with the caveat of not having current measures for all participants in the three original centres, the analyses were repeated with the available measures for cardiovascular risk factors. Additional analyses were conducted using baseline data only, and where possible sensitivity analyses were conducted comparing participants with current measures of cardiovascular risk factors to those without. Vascular factors were included as potential mediators in supplementary analyses of cognitive function with alcohol consumption and smoking as respective exposures.

Methodological covariates

Finally, this section lists covariates pertaining to methodological aspects of the study.

1.) Measurement wave

A dummy variable was created to indicate whether cognitive measures were assessed at baseline or follow-up examination in the three original centres, and used in regression analyses.

2.) Interference with cognitive tests

A dummy variable was created to indicate whether participants experienced vision, hearing or any other problem that could have interfered with cognitive testing. As this data were not collected in the Czech sample, the variable was only used for sensitivity analyses in the remaining centres.

Table 3.7. Complete list of substantive covariates used in statistical analyses

Measure	Description	Type	Coding	Measurement wave
Socio-demographic				
Age	Chronological age in integer years	Continuous	Range 45-78	Baseline/ Wave 2
Education	Highest completed education level	Categorical	See Table 3.6.	Baseline
Household assets	Number of household assets owned	Continuous	See Table 3.6.	Baseline/ Wave 2
Health behaviours				
Alcohol intake	Total alcohol intake in past year	Categorical	See Table 3.6.	Baseline/ Wave 2
Smoking status	Current smoking status	Categorical	See Table 3.6.	Baseline/ Wave 2
Additional health behaviours				
Leisure-time physical activity	How many hours in a typical week [Wave 2 & Kaunas: in summer/winter] do you spend on activities such as sports, hiking, games?	Binary	None vs. some	Baseline/ Wave 2
Health measures				
Self-rated health	Over the last 12 months, would you say your health has been? Very good, Good, Average, Poor, Very poor.	Continuous	Range 1-5	Baseline/ Wave 2
Self-reported medical history				
Myocardial infarction (MI)	Ever been told by a physician you had or were hospitalised for myocardial infarction?	Binary	Yes/No	Baseline/ Wave 2
Angina/Ischemic heart disease (ISH)	Ever been told by a physician you had or were hospitalised for angina/ISH?	Binary	Yes/No	Baseline/ Wave 2
Stroke	Ever been told by a physician you had or were hospitalised for stroke?	Binary	Yes/No	Baseline/ Wave 2
High blood pressure	Have you been told by a physician that you have high blood pressure?	Binary	Yes/No	Baseline/ Wave 2
Diabetes	Have you been told by a physician that you have diabetes?	Binary	Yes/No	Baseline/ Wave 2
Additional health measures				
Baseline depressive symptoms	Presence of depressive symptoms assessed by CES-D 10 on a 4-point scale (binary scale Wave 2 + Kaunas)	Binary	Yes/No	Baseline/ Wave 2
Baseline clinical examination				
Body Mass Index (BMI), (kg/m^2)	Height and weight measured at examination	Continuous		Baseline
Systolic blood pressure, (mmHg)	Average of three measurements using a digital monitor	Continuous		Baseline
Diastolic blood pressure, (mmHg)	Average of three measurements using a digital monitor	Continuous		Baseline
Resting pulse, (bpm)	Average of three measurements using a digital monitor	Continuous		Baseline
High-density lipoproteins, (mmol/L)	Serum concentrations determined using a conventional enzymatic method	Continuous		Baseline
Low-density lipoproteins, (mmol/L)	Serum concentrations determined using a conventional enzymatic method	Continuous		Baseline

3.4. Missing data

Throughout this work complete case analyses were performed, based on listwise deletion on all variables included in the relevant analytic model. While there were generally very little missing data in Kaunas, 22.7% of participants in Czech towns, Novosibirsk and Krakow did not have data on cognitive function. This resulted from a combination of missing by design, since in these centres cognitive function was only assessed in a subset of participants at baseline, and longitudinal attrition in participants who were not eligible for cognitive assessment at baseline and were subsequently lost to follow-up. Additionally, in analysis of life course SEP 40% of Czech participants did not have data on parental education due to longitudinal attrition because the question was only introduced at follow-up.

Suitability of the different methods available for dealing with missing data depends on the underlying missingness mechanism. If data are missing completely at random (MCAR) so that missingness is independent of observed and unobserved values of missing variables, complete case analysis results in unbiased estimates. However, it may still result in a significant loss of power and precision. If instead missingness depends on other observed variables in the dataset but not on the unobserved values of missing variables themselves, the missingness mechanism is missing at random (MAR). Finally, if missingness is also a function of the unobserved values of the variables, the data are missing not at random (MNAR).

In this study MCAR seems unlikely, which is supported by the observation that for most variables used in the analyses the probability of an observation being missing was

significantly correlated with other observed variables in the dataset in all centres. This suggests that the data may be MAR. To evaluate potential bias in complete case estimates from attrition between baseline and follow-up in the three original cohorts, sensitivity analysis was conducted comparing results in participants who had baseline cognitive data but were subsequently lost to follow-up with results in participants who remained in the study.

Finally, MAR and MNAR mechanisms cannot be distinguished empirically because the values of missing observations are by definition unobserved, and it is possible that missingness in this study was the product of an MNAR mechanism. It is imaginable that the probability of a missing observation for cognitive function depends on the value of that observation, if, for example, low functioning individuals or individuals with a high rate of cognitive decline were not able to take part in the study. In the three original cohorts individuals with baseline cognitive data, who were lost to follow-up had lower cognitive scores than individuals, who remained in the study. Unfortunately, other than sensitivity analysis, specific methods for dealing with data missing not at random are currently not widely implemented in commercial statistical software.

3.5. Statistical software

Data preparation, descriptive and inferential statistics were performed in Stata, version 12 (260). Structural equation modelling was conducted in Mplus, version 6.12 (261).

3.6. Statistical analysis

This section describes statistical analyses of life course SEP, alcohol consumption and smoking in relation to cognitive function based on the sample of participants with at least one cognitive measurement.

3.6.1. Life course SEP and cognitive function

This section describes statistical analysis plan for life course SEP and cognitive function.

3.6.1.1. Descriptive analysis

Descriptive statistics were calculated for all variables used in the analysis. T-tests, ANOVAs or chi-square tests were used to test for differences in means and distributions of variables between groups (e.g. centres and sex). Where multiple tests were conducted, or continuous outcomes were compared across three or more levels of a variable appropriate corrections were used. Bonferroni multiple comparisons test was used for post-hoc pairwise comparisons with oneway ANOVA (results from Sidak and Sheffe were also inspected), although it is recognized that these methods may be too conservative.

3.6.1.2. Preliminary regression analysis

Linear regression was used as an initial test of associations between SEP measures from across the life course and cognitive function. Centre and sex-specific z-scores on each individual cognitive test and global cognition were the outcome measures in these analyses. To start with, tests for interactions between SEP measures and centre, and SEP measures and sex were conducted. Statistically significant interactions were observed between SEP and both centre and gender, although the results could have been driven by the high statistical power of the pooled sample. However, preliminary analysis suggested that at least some of these interactions were also substantively important. Subsequently, all analyses were stratified by centre and gender.

Regression analyses with life course SEP measures as predictors and standardized cognitive test scores as outcomes were conducted in several steps. Cognitive test scores were initially regressed on each SEP measure in age-adjusted models. Because of a very high correlation between mother's and father's education in all centres, the variables could not be entered in regression equations simultaneously. Mother's education was hypothesized to be a more important predictor of late life cognition and was thus used in analyses as the main measure of childhood SEP together with the basic amenities scale, a measure of material conditions. However, all analyses were also repeated with father's education.

After these initial analyses, associations between life course SEP measures and cognitive function were estimated sequentially. First, a model with only childhood SEP measures was estimated (Model 1). Educational attainment (Model 2), and household assets (Model 3) were sequentially added to this model. The models with SEP measures from all three life course

stages were then adjusted for two core health-related behaviours (alcohol intake and smoking status, Model 4). Significant reductions in the magnitude of coefficients of SEP measures after adjusting for alcohol consumption and smoking would suggest that these health behaviours mediate the associations between SEP and cognition. Finally, the analyses were additionally adjusted for health measures (self-rated health and medical history, Model 5). All regression analyses were adjusted for age and measurement wave.

3.6.1.3. Structural equation analysis

Following the preliminary regression analyses, structural equation modelling was used to estimate the hypothesized multiple pathways linking life course SEP measures to mid and late life cognitive function. Among advantages of structural equation modelling are that it allows for hypothesized causal and temporal relationships between the variables to be represented explicitly, enables straightforward estimation of indirect and total effects of explanatory variables on the outcome and provides a framework for incorporation of latent variables.

In structural equation analysis the outcome variable was a latent cognitive function construct; confirmatory factor analysis showed substantial common variance shared by the different cognitive measures (verbal memory (immediate recall), verbal fluency and mental speed) thought to reflect a general cognitive factor. These three cognitive tests were chosen because they represent different cognitive domains; there is significant overlap between delayed recall and immediate recall. A potential advantage of using latent variables is that measurement error is explicitly modelled. Multiple indicators may be associated with a single latent

construct, and indicators are not assumed to be perfectly reliable measures of the latent variable but instead the correlations and path coefficients are appropriately adjusted. On the other hand, observed variables are assumed to be measured without error.

Initially, childhood SEP was conceived as a latent factor, comprised of mother's education and basic amenities. However, the association with cognition did not appear to be driven by the latent trait. Consequently, mother's education and childhood amenities were included separately as observed independent variables. Both measures were included in the model because they represent different aspects of childhood socioeconomic environment; parental education is thought to capture cultural resources of the family, while availability of basic amenities measures material conditions in childhood. In addition, structural equation analyses were repeated using father's education in substitute of mother's education. Household asset ownership was used to measure adult SEP because preliminary regression analyses showed it to be more strongly and consistently associated with cognitive function than economic hardship. In addition, a model assuming a latent construct for adult SEP, comprised of household assets and economic hardship, did not appear to adequately describe the data.

The final structural equation model is shown in Figure 3.2. In the structural model, education and household assets were assumed to partially mediate the associations of childhood SEP with cognition, although direct paths from childhood SEP measures to the latent cognitive factor were also estimated. Based on this model, indirect and total effects of childhood SEP measures and education on cognition were estimated. Education was entered as a categorical mediating variable. The model was adjusted for age at cognitive assessment, assuming direct paths leading from age to cognition, assets and education. The model was estimated

conditional on covariances between observed exogenous variables, allowing for residual correlations between childhood SEP measures (education of mother or father and basic amenities in childhood), and between childhood SEP measures and age.

Model fit was assessed using the Comparative Fit Index (CFI), Tucker-Lewis Index (TFI) and Root Mean Square Error of Approximation (RMSEA). CFI and TFI values >0.90 and >0.95 indicate acceptable and good fit, and RMSEA values <0.05 indicate good fit. Because it is known to be overly sensitive to model misspecification with large sample sizes, χ^2 statistic was not used to evaluate model fit. Model estimation employed the robust (mean and

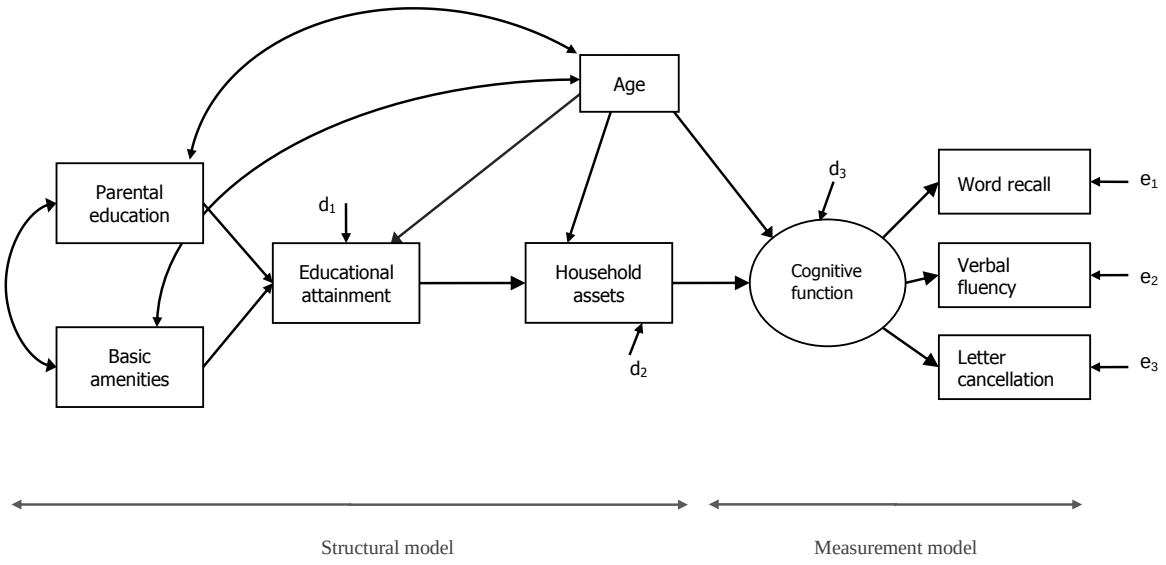

Figure 3.2. Schematic representation of structural equation model of life course SEP and cognitive function
Circles are latent variables, squares are observed variables. Arrows leading from the latent cognitive factor to indicators are factor loadings. Arrows connecting the variables are hypothesized directional effects. Small single-headed arrows pointing to the variables are error terms (e.g. e_1) associated with factor indicators and disturbances (e.g. d_1) associated with endogenous dependent variables. Double-headed curved arrows are residual correlations between exogenous independent variables. Education was entered as a categorical mediating variable; where education is the dependent variable probit regression was used.

variance adjusted) weighted least squares (WLSMV) estimator for categorical dependent variables (own education), which handles missing data using pairwise present (262). The results were compared after listwise deletion on all variables in the model (n=25,127) with those obtained from pairwise present (n=30,846). Methods incorporating missing data are generally thought to be less biased and more efficient than complete case analysis. As preliminary statistical analyses and theoretical considerations suggested a modifying role of study centre and gender, a multiple-group model was specified (centre*gender).

Since a latent cognitive factor was used in a multiple-group set-up, it was necessary to establish that it measured the same underlying construct in all groups (measurement invariance). Three levels of measurement invariance are usually tested. Configural or weak factorial invariance assumes the latent factor has the same structure in each group (the same configuration of factor loadings). Metric or strong factorial invariance imposes an additional assumption of equal factor loadings across groups. This suggests that the latent factor has the same unit or interval of measurement in all groups. Finally, intercept or scalar invariance introduces a further assumption of equal intercepts across groups. This is a necessary condition for comparing latent means across groups, whereas structural parameters may be compared as long as the assumption of equal factor loadings is (at least partially) satisfied (263).

Measurement invariance of the latent cognitive factor was assessed by first fitting the measurement model separately in all groups. Second, multiple-group analysis was used to specify a gradually more restrictive model by first, running a baseline model with all parameters allowed to vary freely, and then, by sequentially constraining factor loadings, and intercepts across groups, and, finally, by adding covariates. If applying parameter constraints

results in a significant deterioration of model fit at any step, then measurement invariance cannot be demonstrated at that level. Measurement invariance was assessed across centres within gender, within centres across gender, and, finally, for the eight-group model (centre*gender).

After establishing measurement invariance for the latent cognitive factor, the full structural equation model was first estimated separately in each group. This was followed by a multiple-group model in all eight groups. Two multiple-group models were estimated. First, a multiple-group model with all structural parameters constrained was used to obtain estimates averaged across groups. Statistically, this should achieve the same goal as a fixed-effects meta-analysis for each model parameter with the advantage of having individual-level data. As a kind of sensitivity analysis, results from the fully constrained multiple-group structural equation model were compared to results from meta-analyses conducted for all structural parameters based on estimates from structural equation models with all parameters freely estimated and fitted separately in each group. Second, to explore differences between groups the fully constrained multiple-group model was compared to the one where all structural parameters were freely estimated in each group. Paths that differed significantly between groups were identified by post-hoc analyses of model fit.

3.6.2. Alcohol and cognitive function

This section describes statistical analysis plan for alcohol consumption and mid-late life cognitive function.

3.6.2.1. Descriptive analysis

Means and standard deviations or frequency distributions were calculated for all variables used in the analytic models. In addition, differences in cognitive function, socioeconomic variables and health measures were tabulated across total alcohol intake categories. The significance of these associations was tested using t-tests, ANOVAs or chi-square tests, as appropriate. Multiple comparisons tests (Bonferroni) were used for multiple testing and post-hoc pair-wise comparisons with ANOVA. Frequency distributions were also calculated for measures of past drinking behaviour in Novosibirsk.

3.6.2.2. Regression analysis

In order to allow comparison, centre and sex-specific standardized z-scores scores on each individual cognitive test were used as outcome measures. A measure of global cognition was derived by averaging z-scores from each cognitive test. Although alcohol*sex interactions were generally not statistically significant, analyses were stratified by gender because men and women had markedly different alcohol consumption patterns.

Associations between alcohol consumption indices and cognitive z-scores were estimated using multiple OLS linear regression, with light drinkers used as a reference group for all alcohol indices. Analyses of cognitive function and alcohol type were restricted to drinkers. The regression models were sequentially adjusted for possible confounders, including age (Model 1), socioeconomic position (education and household assets, Model 2), and smoking status (Model 3), and, additionally, also for health measures (self-rated health and self-reported medical history, Model 4). Regression models for cognitive function and alcohol type were also adjusted for total alcohol volume. Analyses were conducted separately for each study centre and the cohort as a whole, after testing for heterogeneity of relationships between centres (alcohol*centre interactions). Pooled analyses were also adjusted for centre. Possible interactions between alcohol consumption and age were tested by including interaction terms in regression models and also by performing analyses stratified by age group. All regression analyses were additionally adjusted for measurement wave (cognition from baseline vs. follow-up). Additional sensitivity analyses stratified by measurement wave were also conducted.

In supplementary analysis the models were additionally adjusted for two other potential confounders, physical activity and the presence of depressive symptoms. Finally, additional analyses were conducted with further adjustments for cardiovascular risk factors (BMI, systolic and diastolic blood pressure, resting pulse, and high and low-density lipoproteins (all continuous)) measured at baseline clinical examination. Cardiovascular risk factors are plausible mechanisms linking alcohol consumption to cognitive functioning. These analyses had a reduced sample size as a result of relatively large numbers of missing values in the clinical examination measures; not all participants who completed the health questionnaire, attended the clinical examination.

Some of the cognitive tests used may be less sensitive to functioning at high or low levels of cognition, and significant numbers of participants may score at ceiling or floor. In case of ceiling and floor effects Tobit models provide an improvement over simple regression. In this study floor effects seemed unlikely with the proportion of participants scoring at floor never exceeding 1%. Only for delayed recall was there a possibility of significant ceiling effects; for the other cognitive tests the proportion of participants scoring at ceiling was always below 1%. For delayed recall, the proportion of participants scoring at ceiling in the pooled sample was 15.4% (range from 11.1% in Krakow to 19.3% in Kaunas). Analyses of this outcome and alcohol consumption measures were repeated using Tobit regression with delayed recall right-censored at the maximum score of 10.

The same regression modelling strategy was used for analyses of past drinking in Novosibirsk. Again, analyses were gender-stratified and adjusted for relevant confounders; age, socioeconomic position (education and household assets), smoking status and health measures (self-rated health and self-reported medical history). All regression models were adjusted for measurement wave. Regression analyses were performed with participants coded according to their past drinking behaviour, and past drinking behaviour cross-classified by current alcohol consumption with cognitive z-scores as outcomes. In addition, regression analyses of alcohol intake and drinking frequency with cognitive z-scores as outcomes were preformed excluding former drinkers with poor health and reduced use drinkers. Sensitivity analyses were preformed restricted to participants with cognitive measurement from the baseline examination.

3.6.3. Smoking and cognitive function

Following on from the section on alcohol consumption, this section describes statistical analysis plan for separate analyses of smoking behaviour and mid-late life cognitive function.

3.6.3.1. Descriptive analysis

Descriptive analyses were performed and analysis of variance (ANOVA), t-tests and chi square tests used to test for differences in cognitive function, socioeconomic variables and health measures across smoking status categories. Bonferroni adjustment was used for multiple comparisons. Preliminary analysis suggested there were some significant interactions between smoking and sex, and therefore all subsequent analyses were stratified by gender.

3.6.3.2. Regression analysis

OLS multiple linear regression was used to investigate the associations between cognitive function measures and smoking status (categorical variable), and between cognitive function measures and pack years of smoking (continuous variable). In order to allow comparison, centre and sex- specific standardized z-scores on each of the four cognitive tests were used as outcome measures, together with a measure of global cognition, with z-scores averaged across the four cognitive tests. Analyses with pack years were conducted with never smokers

coded as zero, and repeated restricted to current smokers and ever smokers, and with pack years categorized into centre-specific quintiles.

The regression models were sequentially adjusted for potential confounders and other covariates: age-adjusted only (Model 1); socioeconomic variables (education and household assets, Model 2); total alcohol intake (Model 3); and, finally, health measures (self-rated health and medical history variables, Model 4). All models were additionally adjusted for measurement wave (cognition at baseline vs. follow-up), and sensitivity analyses stratified by measurement wave were also conducted. All pooled analyses were adjusted for study centre. Possible interactions between smoking status and age were tested by including interaction terms in regression models and also by performing analyses stratified by age group.

In supplementary analysis the models from the main analysis were additionally adjusted for two other potential confounders, physical activity and the presence of depressive symptoms. Finally, additional analyses were conducted with further adjustments for cardiovascular risk factors (BMI, systolic and diastolic blood pressure, resting pulse, and high and low-density lipoproteins (all continuous)) measured at baseline clinical examination. Cardiovascular risk factors are plausible mechanisms meditating between smoking behaviour and cognitive performance. Analyses with baseline clinical examination data had a reduced sample size as a result of relatively large numbers of missing values in the clinical examination measures; not all participants who completed the health questionnaire, attended the clinical examination. Due to data availability and changes in data collection between survey waves, all supplementary analyses were also conducted restricted only to participants in Czech towns, Novosibirsk and Krakow with cognitive function measured at the 2002-2005 baseline.

Alternative ways of measuring smoking (e.g. reported daily number of cigarettes smoked; alternative categorizations of individuals smoking less than one cigarette daily; distinguishing between long-term ex-smokers and recent quitters) were examined in exploratory analyses.
As with alcohol consumption, due to possible ceiling effects analyses of delayed recall and smoking were repeated using Tobit regression with the cognitive outcome right-censored (at max.=10).

Interactions between smoking status (categorical) and alcohol measured as total alcohol intake (grams per day), drinking frequency and binge drinking (all categorical), respectively, were included in regression models to examine the possibility that effects of smoking on cognitive function are modified by the level of alcohol consumption. For categorical by categorical variable interactions the reference group was never smoker, light/infrequent/non-binge drinker. Three-way interactions between smoking, alcohol and centre were also examined to test for possible heterogeneity of effects across centres. Overall statistical significance of the interaction terms included in the models was assessed using Wald tests. Full models were adjusted for age, socioeconomic covariates and health measures.

Chapter 4. Results

This chapter collates the results of statistical analyses conducted to address the aims of this thesis. The chapter is organized into three sections presenting the results of analyses on cognitive function, and life course SEP (Section 4.1.), alcohol consumption (Section 4.2.) and smoking (Section 4.3.) as exposures of interest, respectively. The section on alcohol and cognitive function includes results from analysis of former drinkers in Novosibirsk. In addition, all sections are subdivided into smaller units. In each section descriptive results are presented first, followed by results from one or more sets of inferential analyses.

4.1. Descriptive results for the study sample

The study total after excluding 171 observations with missing information on age and sex was 35,785 participants. From the study total, 29,212 (81.6%) participants participated in at least one cognitive assessment, and 28,159 (78.7%) had valid data on all four cognitive tests. Corresponding centre-specific numbers with complete data on all cognitive tests were 6,419 (72.9%) in Czech towns, 7,027 (75.3%) in Novosibirsk, 7,955 (74.2%) in Krakow and 6,924 (97.7%) participants in Kaunas. Summary statistics, frequency distributions and proportion of data present for the variables used in the thesis in main or supplementary analyses for the study sample in each centre and all centres combined are shown in Table 4.1.

Table 4.1. Descriptive characteristics of study sample (n=35,785)

	Czech towns (n=8,737)				Novosibirsk (n=9,285)				Krakow (n=10,678)				Kaunas (n=7,085)				Total (n=35,785)			
	N	P (%)	Mean	SD	N	P (%)	Mean	SD	N	P (%)	Mean	SD	N	P (%)	Mean	SD	N	P (%)	Mean	SD
Cognitive measures																				
Word recall	6419	73.5	22.6	(3.6)	7515	80.9	20.9	(4.6)	8061	75.5	20.4	(4.3)	6994	98.7	21.8	(4.1)	28989	81.0	21.3	(4.3)
Verbal fluency	6423	73.5	23.6	(6.6)	7523	81.0	18.8	(7.0)	8070	75.6	20.9	(6.4)	7002	98.8	21.4	(6.1)	29018	81.1	21.1	(6.8)
Letter cancellation	6364	72.8	17.9	(4.7)	6997	75.4	17.3	(5.3)	7957	74.5	17.9	(5.9)	6960	98.2	16.2	(4.8)	28278	79.0	17.3	(5.3)
Delayed recall	6410	73.4	7.6	(1.8)	7513	80.9	7.0	(2.1)	8042	75.3	7.0	(1.9)	6990	98.7	7.7	(1.9)	28955	80.9	7.3	(2.0)
Demographic measures																				
Female, (%)	4707	100	53.4		5085	100	54.5		5498	100	51.2		3866	100	54.6		19156	100	53.3	
Age	8737	100	59.0	(6.9)	9285	100	58.7	(6.8)	10678	100	58.7	(6.3)	7085	100	60.5	(7.6)	35785	100	59.1	(6.9)
Life course SEP measures																				
Childhood SEP																				
Basic amenities at age 10	8121	93.0	4.1	(1.4)	9264	99.8	2.2	(1.7)	10388	97.3	3.3	(1.9)	7071	99.8	3.0	(1.3)	34844	97.4	3.1	(1.8)
Mother's education, (%)		67.1				89.3				99.0				95.5				88.9		
Less than primary	154		2.6		1654		19.8		1085		10.2		1271		18.8		4164		13.2	
Primary	2985		50.7		2819		33.8		5493		51.7		3738		55.3		15035		47.6	
Secondary	2672		45.4		3420		41.0		3583		33.7		1450		21.4		11125		35.2	
University	73		1.2		450		5.4		456		4.3		304		4.5		1283		4.1	
Father's education, (%)		66.1				90.8				98.7				90.6				87.1		
Less than primary	85		1.5		1438		17.0		922		8.7		917		14.3		3362		10.7	
Primary	1357		23.4		2788		32.9		4451		42.0		3456		53.8		12052		38.5	
Secondary	3982		68.7		3460		40.8		4061		38.3		1515		23.6		13018		41.6	
University	376		6.5		794		9.4		1158		10.9		532		8.3		2860		9.1	
Early adult SEP																				
Education, (%)		99.5				100				99.9				99.9				99.8		
Primary	1107		12.6		978		10.5		1238		11.6		891		12.6		4214		11.7	
Secondary	6450		73.6		5662		60.7		6419		59.9		3872		54.7		22403		62.4	
University	1205		13.8		2694		28.9		3060		28.6		2314		32.7		9273		25.8	
Mid-later life SEP																				
Household assets	7948	91.0	6.6	(2.0)	9255	99.7	5.3	(2.1)	10409	97.5	6.3	(2.1)	7025	99.2	6.6	(2.0)	34637	96.8	6.2	(2.1)
Economic deprivation	8617	98.6	10.7	(2.2)	9283	99.9	8.5	(3.4)	10591	99.2	10.1	(2.9)	7048	99.5	11.0	(1.9)	35539	99.3	10.0	(2.9)
Health behaviours																				
Alcohol intake in past year, (%)		97.8				99.9				99.6				99.8				99.3		
Non-drinker	1237		14.5		1508		16.2		3163		29.7		472		6.7		6380		18.0	
Light	4040		47.3		5824		62.7		5277		49.6		4950		70.0		20091		56.5	
Moderate	2514		29.4		1580		17.0		1873		17.6		1450		20.5		7417		20.9	
Heavy	751		8.8		372		4.0		323		3.0		201		2.8		1647		4.6	
Smoking status, (%)		99.2				100				99.8				99.8				99.7		
Never smoker	3808		43.6		5350		57.3		4092		38.2		4442		62.8		17692		49.4	
Current smoker	2243		25.7		2613		28.0		3334		31.1		1361		19.2		9551		26.6	
Former smoker	2688		30.8		1371		14.7		3279		30.6		1269		17.9		8607		24.0	
Physical activity	8482	97.1	70.4		9280	99.9	27.3		10304	96.4	78.0		7068	94.5	49.8		35134	97.1	57.2	

Table 4.1. continued

	N	P (%)	Mean	SD	N	P (%)	Mean	SD	N	P (%)	Mean	SD	N	P (%)	Mean	SD	N	P (%)	Mean	SD
Health measures																				
Self-rated health	8709	99.7	3.4	(0.8)	9285	99.8	2.9	(0.6)	10668	99.9	3.3	(0.8)	7077	99.9	3.1	(0.7)	35739	99.9	3.2	(0.8)
Self-reported medical history																				
Myocardial infarction (MI), (%)	471	95.0	5.6		704	100	7.6		849	99.5	8.0		553	99.8	7.8		2577	98.6	7.3	
Angina/Ischemic heart disease, (%)	744	95.1	8.9		1606	100	17.3		1993	99.2	18.7		701	99.8	9.9		5044	98.5	14.3	
Stroke, (%)	294	94.9	3.5		468	100	5.0		232	99.1	2.2		293	99.8	4.1		1287	98.4	3.6	
High blood pressure, (%)	4204	99.7	48.3		5743	100	61.9		5902	99.8	55.4		4159	99.7	58.9		20008	99.8	56.0	
Diabetes, (%)	1054	99.8	12.1		522	100	5.6		1234	99.8	11.6		539	99.8	7.6		3349	99.9	9.4	
Depressive symptoms, (%)	966	98.1	11.9		1785	99.9	25.5		1749	99.5	17.6		1222	99.8	17.3		5722	99.4	18.2	
Baseline clinical examination																				
Body Mass Index (BMI), (kg/m^2)	7157	81.9	28.3	(4.6)	9284	99.9	28.5	(5.5)	9229	86.4	28.2	(4.6)	7079	99.9	29.4	(5.3)	32749	91.5	28.6	(5.0)
Systolic blood pressure	7150	81.8	139.3	(19.8)	9280	99.9	142.9	(24.7)	9222	86.4	138.4	(21.3)	7058	99.6	139.7	(21.6)	32710	91.4	140.1	(22.1)
Diastolic blood pressure	7150	81.8	88.8	(10.8)	9276	99.9	90.0	(13.3)	9222	86.4	86.3	(11.8)	7058	99.6	89.5	(12.3)	32706	91.4	88.6	(12.3)
Resting pulse	7121	81.5	71.7	(11.9)	9282	99.9	71.5	(11.8)	9179	86.0	73.3	(11.4)	7034	99.3	72.3	(11.4)	32616	91.1	72.2	(11.6)
High-density lipoproteins	6810	77.9	1.4	(0.4)	9253	99.7	1.5	(0.4)	9225	86.4	1.4	(0.4)	6921	99.4	1.5	(0.4)	32209	88.4	1.5	(0.4)
Low-density lipoproteins	6557	75.1	3.5	(0.9)	9146	98.5	4.0	(1.1)	9086	85.1	3.6	(1.0)	6848	96.7	3.8	(1.0)	31637	90.0	3.8	(1.0)

Figures are means with standard deviations (SD) in parentheses or proportions, as appropriate.

P represents proportion of data present for each variable (%).

N is number of observations.

4.2. Life course SEP and cognitive function

This section presents the results from analyses on life course SEP and cognitive function.

4.2.1. Descriptive results

Data on memory, verbal fluency and letter search were available for 28,356 participants. Participants with missing data for cognitive function were younger ($p<0.001$), more likely to be male ($p<0.001$), had lower educational attainment ($p<0.001$), owned fewer assets ($p<0.001$), and had higher values for parental education ($p<0.001$) and childhood amenities ($p<0.001$) than those participants who had cognitive function data. The number of participants with complete data after listwise deletion on all variables used in the structural equation model of life course SEP and cognition was 25,127. Summary statistics and frequency distributions of the study variables used in analysis on life course SEP and cognition, based on complete cases, are presented in Table 4.2.

Average age of participants was 60.0 years in the sample as a whole, and was similar across centres with somewhat greater dispersion of the distribution in Kaunas (age range at Kaunas baseline was 45-72 years). Women made up 53.9% of the sample. Lower mean values were observed in Novosibirsk for measures of childhood and current material circumstances (all two sample t-tests $p<0.001$) than in the other study centres, consistent with generally poorer socioeconomic conditions in Russia. Participants in these cohorts had relatively high levels of education. Educational level was lower in Czech towns than in the other centres, most likely

as a result of differences in the degree of urbanisation (six smaller towns made up the Czech sample, whereas Novosibirsk, Krakow and Kaunas are important regional urban centres). Participants' average educational level was markedly higher than that of their mothers' (and fathers'), undoubtedly a consequence of educational expansion which occurred in the post-war period. In the Czech sample participants' mothers were less likely than mothers in the other centres to have no formal education but the proportion with university education was also comparably smaller. There were significant differences in educational level between men and women across centres, with higher proportions of men having university education; the difference was greatest in the Czech sample (chi square $p<0.001$), and smallest in Kaunas (chi square $p=0.014$). Men in all centres also reported owning a higher mean number of household assets than women (two sample t-tests $p<0.001$ for all centres), perhaps partly a result of a higher proportion of women in the sample being widowed, single or living alone.

Table 4.2. Descriptive characteristics of study sample for life course SEP and cognition (based on listwise deletion, n=25,127)

	Men								Women							
	Czech towns (n=2,203)		Novosibirsk (n=2,747)		Krakow (n=3,661)		Kaunas (n=2,966)		Czech towns (n=2,603)		Novosibirsk (n=3,421)		Krakow (n=3,890)		Kaunas (n=3,636)	
Cognitive measures																
Mean word recall	21.9	(3.5)	20.6	(4.6)	19.9	(4.2)	20.9	(4.1)	23.5	(3.4)	21.8	(4.3)	21.0	(4.2)	22.7	(3.7)
Mean verbal fluency	24.1	(6.7)	19.4	(7.2)	21.0	(6.4)	21.6	(6.0)	24.2	(6.3)	19.1	(6.9)	21.0	(6.3)	21.5	(6.1)
Mean letter cancellation	17.5	(4.6)	16.7	(5.1)	17.5	(5.7)	15.5	(4.6)	18.6	(4.6)	18.1	(5.4)	18.4	(5.9)	16.8	(4.8)
Demographic covariates																
Mean age	60.4	(6.5)	59.4	(6.4)	60.5	(5.5)	60.5	(7.6)	59.5	(6.4)	59.2	(6.4)	59.9	(5.7)	60.2	(7.6)
Life course SEP measures																
Childhood SEP																
Mean no. of childhood amenities	4.0	(1.4)	2.2	(1.7)	3.2	(1.9)	3.0	(1.3)	4.1	(1.4)	2.3	(1.6)	3.3	(1.9)	3.0	(1.3)
Mother's education, (%)																
Less than primary	2.2		19.4		11.0		17.4		2.7		21.4		10.2		19.6	
Primary	51.2		33.6		52.3		55.7		50.3		32.9		53.0		55.1	
Secondary	44.9		41.2		32.8		21.7		46.0		41.1		32.5		21.2	
University	1.6		5.9		4.0		5.2		1.0		4.6		4.2		4.0	
Adult SEP																
Education, (%)																
Primary	3.7		10.5		9.1		12.2		14.5		8.7		13.7		10.6	
Secondary	74.4		54.5		59.1		52.8		73.8		62.4		58.9		56.1	
University	21.9		34.9		31.9		35.0		11.8		28.9		27.4		33.3	
Mid-late life SEP																
Mean no. of household assets	7.1	(1.9)	5.7	(2.1)	6.6	(2.1)	7.1	(2.0)	6.6	(1.9)	5.3	(2.1)	6.0	(2.1)	6.3	(2.0)

Figures are means with standard deviations in parentheses or proportions, as appropriate.

4.2.2. Preliminary regression analysis

Preliminary regression analyses indicated significant heterogeneity between centres in associations of SEP measures and cognitive outcomes, with interactions generally significant at 1% level. In addition, statistically significant heterogeneity was observed between genders for some combinations of SEP measures and cognitive function, usually involving own education or household assets and verbal fluency or letter search. Subsequently, analyses were performed stratified by centre and gender.

Detailed results from preliminary regression analyses are shown in Appendix III, starting on pg. 250. Estimates of direct effects of SEP measures on cognition from regression analyses should correspond to results from structural equation modelling, save for minor discrepancies resulting from differences in assumptions and model specification. Therefore, only structural equation modelling results are discussed in detail in this section. However, some additional findings resulting from regression analyses are worth noting and are thus presented briefly in this section.

For regression analyses of associations between life course SEP measures and cognition there were 23,888 participants with complete data on all variables used in the models: cognitive function (z-transformed cognitive test scores and global cognition), life course SEP measures, health-related behaviours and health status measures. In age-adjusted models all SEP measures were significantly associated with all cognitive tests and global cognition across centres and genders, with the exception of non-significant associations between childhood amenities with verbal fluency and letter search as outcomes in Novosibirsk men. In these

Table 4.3. Regression results for life course SEP and global cognition, before and after adjusting for alcohol intake and smoking

	Men				Women			
	Global cognition				Global cognition			
	Mutually-adjusted		Health behaviours		Mutually-adjusted		Health behaviours	
	b	SE	b	SE	b	SE	b	SE
Czech towns								
Mother's education								
Less than primary	0.00		0.00		0.00		0.00	
Primary	0.15	(0.11)	0.12	(0.11)	0.31***	(0.08)	0.30***	(0.08)
Secondary	0.31**	(0.11)	0.28**	(0.11)	0.43***	(0.09)	0.42***	(0.09)
University	0.32*	(0.15)	0.30*	(0.15)	0.54***	(0.15)	0.53***	(0.15)
Childhood amenities	0.01	(0.01)	0.01	(0.01)	-0.00	(0.01)	-0.00	(0.01)
Education								
Primary	0.00		0.00		0.00		0.00	
Secondary	0.46***	(0.08)	0.46***	(0.08)	0.50***	(0.04)	0.48***	(0.04)
University	0.81***	(0.08)	0.80***	(0.08)	0.83***	(0.05)	0.81***	(0.05)
Household assets	0.04***	(0.01)	0.04***	(0.01)	0.03***	(0.01)	0.02**	(0.01)
N	**2048**		**2048**		**2376**		**2376**	
Novosibirsk								
Mother's education								
Less than primary	0.00		0.00		0.00		0.00	
Primary	0.07	(0.03)	0.07	(0.03)	0.10***	(0.03)	0.10***	(0.03)
Secondary	0.08*	(0.04)	0.08*	(0.04)	0.18***	(0.03)	0.17***	(0.03)
University	0.20***	(0.06)	0.20***	(0.06)	0.18**	(0.06)	0.18***	(0.05)
Childhood amenities	0.01	(0.01)	0.01	(0.01)	0.02**	(0.01)	0.02**	(0.01)
Education								
Primary	0.00		0.00		0.00		0.00	
Secondary	0.18***	(0.04)	0.18***	(0.04)	0.26***	(0.04)	0.26***	(0.04)
University	0.47***	(0.05)	0.46***	(0.05)	0.54***	(0.04)	0.54***	(0.04)
Household assets	0.06***	(0.01)	0.06***	(0.01)	0.05***	(0.01)	0.05***	(0.01)
N	**2655**		**2655**		**3285**		**3285**	
Krakow								
Mother's education								
Less than primary	0.00		0.00		0.00		0.00	
Primary	0.12***	(0.04)	0.11**	(0.04)	0.17***	(0.04)	0.16***	(0.04)
Secondary	0.19***	(0.04)	0.18***	(0.04)	0.20***	(0.04)	0.19***	(0.04)
University	0.27***	(0.07)	0.27***	(0.07)	0.30***	(0.07)	0.28***	(0.07)
Childhood amenities	0.02**	(0.01)	0.02**	(0.01)	0.02**	(0.01)	0.02*	(0.01)
Education								
Primary	0.00		0.00		0.00		0.00	
Secondary	0.22***	(0.04)	0.21***	(0.04)	0.33***	(0.03)	0.31***	(0.03)
University	0.55***	(0.05)	0.53***	(0.05)	0.68***	(0.04)	0.63***	(0.04)
Household assets	0.06***	(0.01)	0.06***	(0.01)	0.03***	(0.01)	0.02***	(0.01)
N	**3567**		**3567**		**3778**		**3778**	
Kaunas								
Mother's education								
Less than primary	0.00		0.00		0.00		0.00	
Primary	0.05	(0.03)	0.05	(0.03)	0.05	(0.03)	0.05	(0.03)
Secondary	0.12**	(0.04)	0.12**	(0.04)	0.10**	(0.04)	0.10**	(0.04)
University	0.18**	(0.06)	0.18**	(0.06)	0.12	(0.06)	0.12*	(0.06)
Childhood amenities	-0.01	(0.01)	-0.01	(0.01)	-0.01	(0.01)	-0.01	(0.01)
Education								
Primary	0.00		0.00		0.00		0.00	
Secondary	0.38***	(0.04)	0.38***	(0.04)	0.51***	(0.04)	0.50***	(0.04)
University	0.75***	(0.04)	0.75***	(0.04)	0.89***	(0.04)	0.88***	(0.04)
Household assets	0.04***	(0.01)	0.03***	(0.01)	0.03***	(0.01)	0.03***	(0.01)
N	**2790**		**2790**		**3389**		**3389**	

b=regression coefficient; SE=standard error

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Model 1: Adjusted for age and measurement wave.

Model 2: Adjusted for age, alcohol intake, smoking and measurement wave.

Reference group is "primary level or less" for own education and "less than primary level" for mother's education.

models both own education and mother's (and father's) education showed a graded positive relationship with cognitive performance.

Results from mutually adjusted models and models further adjusted for two core health behaviours, alcohol intake and smoking, with global cognition (averaged z-scores across all four cognitive tests) as the outcome are shown in Table 4.3. Results for the other cognitive tests were similar and are shown in Appendix III in Table III-3 and Table III-4 for men and women, respectively. In mutually adjusted models the coefficients for SEP measures were generally significantly reduced compared to models adjusted only for age, most notably for childhood SEP measures and least notably for own education. In contrast, associations between life course SEP measures and cognitive function were largely unaffected by further adjustments for the two core health-related behaviours; across centres coefficients for all SEP measures remained largely unchanged or were attenuated only slightly. This suggests that both alcohol consumption and smoking are unlikely to be important mediators of the associations between SEP and cognition in these populations.

Further adjustments for health measures resulted in only a slight attenuation in the associations between mother's education, education and household assets, and cognitive performance (see Appendix III). Similar results were obtained in additional analyses also controlling for physical activity and depressive symptoms. Among health measures, only self-rated health and history of stroke were consistently associated with cognitive function, in positive and inverse directions, respectively. Since adjustments for health behaviours as well as health measures had only a very limited impact on the associations between SEP measures from across the life course and cognitive function, they were not included as potential mediators or confounders in structural equation analysis.

4.2.3. Structural equation modelling

The number of participants with complete data on all variables used in analysis on life course SEP and cognition was 25,127, and 30,846 after including missing data with pairwise present in structural equation analysis.

Table 4.4. Zero-order correlations among variables used in structural equation models (based on listwise deletion, n=25,127)

	1	2	3	4	5	6	7	8
Czech towns								
1 Word recall	**1**	0.41	0.25	0.23	0.19	0.39	0.21	-0.27
2 Verbal fluency	0.41	**1**	0.31	0.22	0.18	0.42	0.19	-0.24
3 Letter search	0.28	0.35	**1**	0.13	0.13	0.20	0.12	-0.17
4 Mother's education	0.19	0.19	0.13	**1**	0.33	0.33	0.21	-0.22
5 Childhood amenities	0.15	0.14	0.12	0.29	**1**	0.28	0.26	-0.47
6 Education	0.33	0.27	0.24	0.25	0.18	**1**	0.31	-0.16
7 Assets	0.18	0.18	0.12	0.19	0.22	0.29	**1**	-0.32
8 Age	-0.23	-0.17	-0.16	-0.22	-0.46	-0.03	-0.23	**1**
n_m=2203; n_f=2603								
Novosibirsk								
1 Word recall	**1**	0.48	0.35	0.29	0.32	0.36	0.36	-0.43
2 Verbal fluency	0.48	**1**	0.35	0.27	0.21	0.35	0.33	-0.39
3 Letter search	0.37	0.39	**1**	0.16	0.22	0.26	0.28	-0.32
4 Mother's education	0.25	0.22	0.19	**1**	0.31	0.40	0.29	-0.31
5 Childhood amenities	0.28	0.17	0.17	0.33	**1**	0.24	0.29	-0.44
6 Education	0.27	0.27	0.31	0.35	0.16	**1**	0.32	-0.23
7 Assets	0.33	0.33	0.30	0.26	0.22	0.34	**1**	-0.45
8 Age	-0.43	-0.39	-0.31	-0.33	-0.44	-0.14	-0.39	**1**
n_m=2747; n_f=3421								
Krakow								
1 Word recall	**1**	0.55	0.35	0.24	0.29	0.41	0.30	-0.37
2 Verbal fluency	0.54	**1**	0.44	0.28	0.26	0.39	0.22	-0.30
3 Letter search	0.34	0.42	**1**	0.20	0.20	0.29	0.21	-0.20
4 Mother's education	0.25	0.23	0.21	**1**	0.45	0.46	0.26	-0.21
5 Childhood amenities	0.26	0.25	0.19	0.45	**1**	0.40	0.31	-0.38
6 Education	0.36	0.33	0.28	0.40	0.31	**1**	0.39	-0.19
7 Assets	0.30	0.28	0.24	0.27	0.28	0.40	**1**	-0.33
8 Age	-0.34	-0.26	-0.15	-0.23	-0.40	-0.06	-0.23	**1**
n_m=3661; n_f=3890								
Kaunas								
1 Word recall	**1**	0.42	0.36	0.26	0.22	0.45	0.28	-0.37
2 Verbal fluency	0.38	**1**	0.41	0.22	0.20	0.40	0.20	-0.31
3 Letter search	0.35	0.40	**1**	0.21	0.21	0.39	0.25	-0.32
4 Mother's education	0.25	0.18	0.28	**1**	0.40	0.42	0.27	-0.34
5 Childhood amenities	0.21	0.13	0.21	0.39	**1**	0.29	0.29	-0.50
6 Education	0.39	0.32	0.41	0.40	0.21	**1**	0.34	-0.28
7 Assets	0.26	0.16	0.24	0.23	0.22	0.33	**1**	-0.36
8 Age	-0.37	-0.26	-0.30	-0.33	-0.49	-0.16	-0.27	**1**
n_m=2966; n_f=3636								

Figures are Pearson correlations for combinations of continuous variables and polyserial correlations for combinations of continuous and categorical (participants' education) variables, as treated in structural equation models.
Correlations for men and women (shaded) are below and above the diagonal, respectively.

Zero-order correlations among the variables used in structural equation analysis are shown in Table 4.4. The intercorrelations for the cognitive tests were significant and mostly similar across centres, ranging from 0.28 ($p<0.001$) for memory and letter search in Czechs to 0.54 ($p<0.001$) for verbal fluency and memory in Krakow.

Across centres, all SEP variables were significantly correlated with all cognitive functions, with higher SEP values positively covarying with higher cognitive scores. Across centres SEP measures from each stage of the life course were significantly and positively correlated with SEP measures from all other life course stages. Expectedly, age was negatively correlated with all cognitive functions. Inverse correlations were also observed between age and all SEP measures.

Structural equation models were estimated for complete cases (listwise deletion, n=25,127) and after including missing data (pairwise present, n=30,846). The results were very similar; therefore results only from the latter are reported. Measurement invariance testing supported invariance of factor loadings but not invariance of intercepts across groups (further details are given in Appendix IV, pg. 256). Invariance of factor loadings is sufficient for comparison of structural parameters across groups, the primary focus of this study.

Direct estimates for the model with all structural paths constrained across groups are reported in Figure 4.1. Indirect and total effects are shown in Table 4.5. Unstandardized estimates are preferred for comparing groups because different variances between groups may lead to different standardized estimates even with the same unstandardized solution. For this reason only unstandardized effects are reported for the model with path coefficients constrained

across groups, and both unstandardized and standardized effects are reported for the unconstrained multiple-group model.

The fully constrained multiple-group model had an adequate fit to the data (χ^2=1326.335, df=178; CFI=0.954; TLI=0.949; RMSEA=0.041 [0.039-0.043]). This model revealed that SEP measures from all stages of the life course were significantly (p<0.001) associated with cognition in mid and later life. Only childhood amenities were not substantively associated with cognition (p=0.013) in this model.

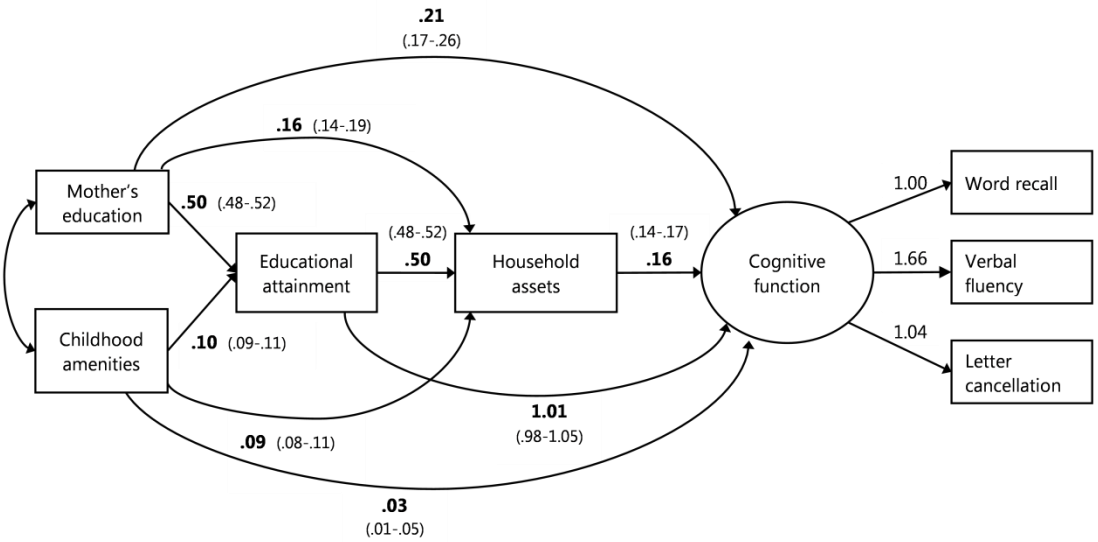

Figure 4.1. Estimates from constrained multiple-group structural equation model
The figure shows unstandardized path coefficients with 95% CIs from the multiple-group structural equation model with all structural parameters constrained across groups representing pathways between childhood SEP, educational attainment, adult household assets, and cognitive function (n=30,846; χ2=1326.335, df=178; CFI=0.954; TLI=0.949; RMSEA=0.041 [0.039-0.043]). Educational attainment is entered as a categorical mediator; paths leading to it are probit coefficients. The model is age-adjusted with direct paths from age to cognition, assets and education, and estimated conditional on the covariances (↔) between observed exogenous variables (childhood SEP measures and age) but, for clarity, age and paths associated with it are not shown in the figure.

Among the life course SEP measures the strongest direct path to cognition was from own education. The indirect path leading from own education to cognition via household asset ownership was very small. A comparably weaker direct path to cognition was from household asset ownership, a measure of current SEP.

Although statistically significant, the direct path from mother's education to the latent cognitive factor was weak. Additionally, mother's education showed a significant indirect association with cognition, largely mediated through its effect on participants' own education. The indirect effect of mother's education on cognition was greater than its direct effect.

Table 4.5. Estimates of indirect and total effects of life course SEP measures on cognition from constrained multiple-group structural equation model (n=30,846)

	Constrained model		
	b	**SE**	**p-value**
Indirect effects on cognition			
Mother's education → Education	0.51	0.02	<0.001
Mother's education → Assets	0.03	0.00	<0.001
Mother's education → Education → Assets	0.04	0.00	<0.001
Total indirect effect Mother's education → Cognition	0.57	0.02	<0.001
Childhood amenities → Education	0.10	0.01	<0.001
Childhood amenities → Household assets	0.02	0.00	<0.001
Childhood amenities → Education → Household assets	0.01	0.00	<0.001
Total indirect effect Childhood amenities → Cognition	0.13	0.01	<0.001
Education → Household assets	0.08	0.01	<0.001
Total effects on cognition			
Mother's education	0.78	0.03	<0.001
Childhood amenities	0.16	0.01	<0.001
Education	1.09	0.02	<0.001
Household assets	0.16	0.01	<0.001

b=path coefficient; SE=standard error
Model fit indices: $\chi^2(178)=1326.335$; CFI=0.954; TLI=0.949; RMSEA=0.041 [0.039-0.043]

The total indirect effect of basic childhood amenities on cognition was rather small. Again, it was conveyed primarily via participants' education; the indirect effect conveyed through household assets was negligible. Taking the total effects of SEP measures on cognition into

consideration, mother's education came second to participants' own education, followed by the total effects of household assets currently owned and basic amenities in childhood, which were of similar magnitude.

The unconstrained model was a significant improvement over the fully constrained model (χ^2 (94) = 621.824, RMSEA=0.038 [0.035-0.041]; CFI=0.979; TLI=0.955), suggesting that there were some significant group differences. Post-hoc evaluation of model fit identified parameters that differed significantly across groups. Estimates for the unconstrained model are reported in Table 4.6. and Table 4.7. for men and women, respectively.

The path from assets to cognition was stronger in Krakow and, especially, Novosibirsk than in Kaunas and Czech towns. Household asset ownership tended to be more strongly associated with cognition in men than in women; this was especially apparent in Polish and Czech samples. The direct path from childhood amenities to cognition was statistically significant in Russian women and at least as important as the path from mother's education. Mother's education was more strongly associated with cognition in Czechs compared to other study centres. The direct path from education was the weakest in Novosibirsk and strongest in Kaunas, and both were significantly different from the average effect of own education estimated in the fully constrained model.

With respect to total effects on cognition, the number of household assets rather than mother's education was second to own education in Novosibirsk men. Total effect of childhood amenities on cognition was not significant in Kaunas but, relative to other SEP measures and compared to other groups, it was larger in Russian women and in Krakow. In Czech women the indirect effect of own education via household assets was not statistically significant.

There was also significant variation in the total effect of education on cognition across centres, partly reflecting variation in the direct effect of education.

When structural equation analysis was repeated using father's education the pattern of results was the same but mother's education was slightly more strongly associated with cognition in men, especially among Czechs, whereas father's education was slightly more strongly associated with cognition in Krakow (the results are shown in Table V-1 of Appendix V, pg. 257). As for mother's education, the total effect of father's education on cognition was significant in all centres, although its magnitude was not substantial. Education of both parents could not be modelled simultaneously because educational homogamy in these cohorts was very high (polychoric correlations for mother's and father's education ranged from 0.92 in Krakow to 0.64 in Czech towns).

Table 4.6. Results from unconstrained multiple-group structural equation model in men

	Czech towns (n=2,499)				Novosibirsk (n=3,789)				Krakow (n=5,036)				Kaunas (n=3,054)			
	b	**SE**	**p-value**	**Std.**	**b**	**SE**	**p-value**	**Std.**	**b**	**SE**	**p-value**	**Std.**	**b**	**SE**	**p-value**	**Std.**
Direct effects on cognition																
Mother's education	0.49	0.11	<0.001	0.12	0.12	0.08	0.112	0.03	0.26	0.08	0.001	0.06	0.14	0.08	0.063	0.04
Childhood amenities	-0.02	0.05	0.697	-0.01	0.05	0.04	0.236	0.03	0.08	0.03	0.016	0.05	-0.07	0.05	0.120	-0.04
Education	0.94	0.07	<0.001	0.42	0.82	0.07	<0.001	0.29	0.94	0.06	<0.001	0.36	1.13	0.06	<0.001	0.50
Household assets	0.09	0.03	0.003	0.08	0.30	0.03	<0.001	0.21	0.24	0.03	<0.001	0.17	0.11	0.03	<0.001	0.09
Direct effects on household assets																
Mother's education	0.23	0.07	0.001	0.07	0.13	0.05	0.006	0.06	0.17	0.05	0.001	0.06	0.07	0.05	0.170	0.03
Childhood amenities	0.10	0.03	0.001	0.07	0.03	0.02	0.281	0.02	0.09	0.02	<0.001	0.08	0.10	0.03	0.002	0.06
Education	0.46	0.05	<0.001	0.26	0.51	0.04	<0.001	0.27	0.65	0.04	<0.001	0.34	0.50	0.04	<0.001	0.28
Direct effects on education																
Mother's education	0.41	0.05	<0.001	0.22	0.41	0.03	<0.001	0.33	0.52	0.03	<0.001	0.34	0.54	0.03	<0.001	0.37
Childhood amenities	0.11	0.02	<0.001	0.15	0.03	0.02	0.086	0.04	0.12	0.01	<0.001	0.20	0.05	0.02	0.015	0.06
Indirect effects on cognition																
Mother's education → Education	0.41	0.05	<0.001	0.10	0.38	0.04	<0.001	0.11	0.50	0.04	<0.001	0.12	0.61	0.05	<0.001	0.18
Mother's education. → Assets	0.02	0.01	0.034	0.01	0.05	0.01	<0.001	0.01	0.03	0.01	0.016	0.01	0.01	0.01	0.159	0.00
Mother's education → Education → Assets	0.02	0.01	0.005	0.01	0.07	0.01	<0.001	0.02	0.09	0.01	<0.001	0.02	0.03	0.01	<0.001	0.01
Total indirect	0.45	0.06	<0.001	0.11	0.50	0.04	<0.001	0.14	0.62	0.04	<0.001	0.15	0.65	0.05	<0.001	0.20
Amenities → Education	0.11	0.02	<0.001	0.06	0.03	0.01	0.007	0.02	0.12	0.01	<0.001	0.07	0.06	0.02	0.011	0.03
Amenities → Assets	0.01	0.00	0.025	0.01	0.01	0.01	0.068	0.01	0.02	0.01	<0.001	0.02	0.01	0.00	0.013	0.01
Amenities → Education → Assets	0.01	0.00	0.009	0.00	0.01	0.00	0.009	0.00	0.02	0.00	<0.001	0.01	0.00	0.00	0.028	0.00
Total indirect	0.12	0.02	<0.001	0.07	0.05	0.01	0.001	0.03	0.16	0.01	<0.001	0.10	0.08	0.03	0.003	0.04
Education → Assets	0.04	0.02	0.003	0.02	0.15	0.02	<0.001	0.06	0.17	0.02	<0.001	0.06	0.06	0.01	<0.001	0.03
Total effects on cognition																
Mother's education	0.94	0.11	<0.001	0.23	0.56	0.07	<0.001	0.16	0.93	0.08	<0.001	0.22	0.78	0.07	<0.001	0.24
Childhood amenities	0.10	0.05	0.036	0.06	0.09	0.04	0.018	0.05	0.24	0.03	<0.001	0.15	0.00	0.05	0.980	0.00
Education	0.98	0.07	<0.001	0.44	1.00	0.06	<0.001	0.36	1.11	0.06	<0.001	0.41	1.21	0.06	<0.001	0.53
Household assets	0.09	0.03	0.003	0.08	0.30	0.03	<0.001	0.21	0.24	0.03	<0.001	0.17	0.11	0.03	<0.001	0.09

Fit indices: $\chi^2(94) = 621.824$, RMSEA=0.038 [0.035-0.041]; CFI=0.979; TLI=0.955

b and Std. denote unstandardized and standardized path coefficients; SE=standard error

Paths from mother's education and childhood amenities to own education are probit coefficients

Table 4.7. Results from unconstrained multiple-group structural equation model in women

	Czech towns (n=2,991)				Novosibirsk (n=4,488)				Krakow (n=5,281)				Kaunas (n=3,708)			
	b	**SE**	**p-value**	**Std.**	**b**	**SE**	**p-value**	**Std.**	**b**	**SE**	**p-value**	**Std.**	**b**	**SE**	**p-value**	**Std.**
Direct effects on cognition																
Mother's education	0.42	0.10	<0.001	0.11	0.20	0.07	0.002	0.06	0.30	0.08	<0.001	0.07	0.02	0.07	0.743	0.01
Childhood amenities	-0.07	0.05	0.113	-0.04	0.12	0.03	<0.001	0.07	0.05	0.03	0.130	0.03	-0.06	0.04	0.117	-0.03
Education	1.05	0.06	<0.001	0.52	0.81	0.06	<0.001	0.32	1.05	0.06	<0.001	0.40	1.19	0.05	<0.001	0.54
Household assets	0.04	0.03	0.132	0.04	0.26	0.03	<0.001	0.19	0.10	0.03	<0.001	0.07	0.10	0.02	<0.001	0.08
Direct effects on household assets																
Mother's education	0.21	0.07	0.001	0.06	0.21	0.04	<0.001	0.08	0.12	0.05	0.015	0.04	0.19	0.05	<0.001	0.07
Childhood amenities	0.09	0.03	0.004	0.06	0.08	0.02	<0.001	0.07	0.10	0.02	<0.001	0.09	0.14	0.03	<0.001	0.09
Education	0.41	0.04	<0.001	0.23	0.38	0.04	<0.001	0.20	0.52	0.04	<0.001	0.29	0.40	0.04	<0.001	0.22
Direct effects on education																
Mother's education	0.51	0.04	<0.001	0.27	0.45	0.03	<0.001	0.35	0.57	0.03	<0.001	0.35	0.51	0.03	<0.001	0.34
Childhood amenities	0.15	0.02	<0.001	0.19	0.07	0.02	<0.001	0.10	0.15	0.01	<0.001	0.24	0.09	0.02	<0.001	0.10
Indirect effects on cognition																
Mother's education → Education	0.55	0.05	<0.001	0.14	0.36	0.03	<0.001	0.11	0.61	0.04	<0.001	0.14	0.62	0.04	<0.001	0.19
Mother's education → Assets	0.01	0.01	0.179	0.00	0.06	0.01	<0.001	0.02	0.01	0.01	0.036	0.00	0.02	0.01	0.008	0.01
Mother's education → Education → Assets	0.01	0.01	0.118	0.00	0.05	0.01	<0.001	0.01	0.03	0.01	<0.001	0.01	0.02	0.01	<0.001	0.01
Total indirect	0.57	0.05	<0.001	0.15	0.47	0.03	<0.001	0.14	0.65	0.04	<0.001	0.15	0.66	0.04	<0.001	0.20
Amenities → Education	0.16	0.02	<0.001	0.10	0.05	0.01	<0.001	0.03	0.01	0.00	0.001	0.01	0.11	0.02	<0.001	0.05
Amenities → Assets	0.00	0.00	0.168	0.00	0.02	0.01	<0.001	0.01	0.01	0.00	<0.001	0.01	0.01	0.00	0.002	0.01
Amenities → Education → Assets	0.00	0.00	0.121	0.00	0.01	0.00	<0.001	0.00	0.05	0.03	0.130	0.03	0.00	0.00	0.002	0.00
Total indirect	0.17	0.02	<0.001	0.10	0.07	0.01	<0.001	0.04	0.18	0.01	<0.001	0.11	0.13	0.02	<0.001	0.06
Education → Assets	0.02	0.01	0.115	0.01	0.10	0.01	<0.001	0.04	0.06	0.01	<0.001	0.02	0.04	0.01	<0.001	0.02
Total effects on cognition																
Mother's education	1.00	0.09	<0.001	0.26	0.65	0.06	<0.001	0.19	0.95	0.08	<0.001	0.22	0.70	0.07	<0.001	0.21
Childhood amenities	0.12	0.04	0.008	0.07	0.22	0.03	<0.001	0.13	0.23	0.03	<0.001	0.14	0.06	0.04	0.160	0.03
Education	1.06	0.06	<0.001	0.52	0.92	0.06	<0.001	0.35	1.11	0.06	<0.001	0.42	1.26	0.05	<0.001	0.56
Household assets	0.04	0.03	0.132	0.04	0.26	0.03	<0.001	0.19	0.10	0.03	<0.001	0.07	0.10	0.02	<0.001	0.08

Fit indices: $\chi^2(94) = 621.824$, RMSEA=0.038 [0.035-0.041]; CFI=0.979; TLI=0.955

b and Std. denote unstandardized and standardized path coefficients; SE=standard error

Paths from mother's education and childhood amenities to own education are probit coefficients

Results for associations between SEP measures at different stages of life course were noteworthy. Own education was significantly influenced by mother's education. The effect was largely similar across study centres. The results for father's education were also very similar (shown in Appendix V). Childhood amenities had a small direct effect on own education. Current household asset ownership received mostly significant but small direct inputs from childhood amenities and mother's education (but generally not father's education), with little variation across study centres. Own education had a moderate effect on current asset ownership, and the effect was stronger in men than in women. The effect of education on household asset ownership was especially strong in Krakow.

Finally, the structural equation analysis was repeated with each of the three cognitive measures as the outcome, as shown in Table 4.8. The pattern of results was generally the same as that observed for the latent cognitive factor in each respective centre. The strongest path to each cognitive outcome was from education, followed by a weaker path from household assets. Notably, in all centres the path from own education was stronger for verbal fluency than for the other two cognitive tests. For the most part, the association between mother's education and verbal fluency was also somewhat stronger relative to word recall and letter cancellation. Mother's education generally had a small significant effect on verbal cognitive measures in women, while it was mostly significantly associated with letter search in men. Childhood amenities had a significant but small direct effect ($p<0.001$) on verbal memory in Novosibirsk, and, additionally, on letter search in Novosibirsk women but not in any of the other centres.

Table 4.8. Direct effects from unconstrained multiple-group structural equation models for each cognitive outcome

	Czech towns				Novosibirsk				Krakow				Kaunas			
	b	SE	p-value	Std.	b	SE	p-value	Std.	b	SE	p-value	Std.	b	SE	p-value	Std.
Men																
Word recall																
Mother's education → Word recall	0.47	0.13	<0.001	0.08	0.09	0.10	0.360	0.02	0.23	0.10	0.027	0.04	0.10	0.11	0.350	0.02
Childhood amenities → Word recall	-0.06	0.06	0.339	-0.02	0.22	0.05	<0.001	0.08	0.04	0.04	0.287	0.02	-0.09	0.06	0.182	-0.03
Education → Word recall	0.97	0.09	<0.001	0.29	0.73	0.09	<0.001	0.17	1.08	0.08	<0.001	0.28	1.18	0.08	<0.001	0.31
Assets → Word recall	0.09	0.04	0.027	0.05	0.28	0.04	<0.001	0.13	0.24	0.03	<0.001	0.12	0.18	0.04	<0.001	0.09
Verbal fluency																
Mother's education → Verbal fluency	1.00	0.25	<0.001	0.08	0.21	0.16	0.203	0.02	0.42	0.16	0.008	0.05	0.02	0.16	0.887	0.00
Childhood amenities → Verbal fluency	0.02	0.11	0.862	0.00	-0.12	0.08	0.123	-0.03	0.16	0.06	0.010	0.05	-0.22	0.10	0.023	-0.05
Education → Verbal fluency	1.47	0.17	<0.001	0.23	1.19	0.15	<0.001	0.18	1.40	0.12	<0.001	0.24	1.57	0.12	<0.001	0.28
Assets → Verbal fluency	0.24	0.08	0.002	0.07	0.52	0.07	<0.001	0.15	0.36	0.05	<0.001	0.12	0.07	0.06	0.223	0.02
Letter cancellation																
Mother's education → Letter cancellation	0.42	0.17	0.017	0.05	-0.08	0.12	0.536	-0.01	0.57	0.14	<0.001	0.07	0.39	0.12	0.001	0.06
Childhood amenities → Letter cancellation	0.01	0.08	0.860	0.00	0.00	0.06	0.958	0.00	0.10	0.06	0.085	0.03	0.01	0.07	0.855	0.00
Education → Letter cancellation	0.96	0.11	<0.001	0.22	1.13	0.10	<0.001	0.24	0.97	0.10	<0.001	0.19	1.43	0.09	<0.001	0.34
Assets → Letter cancellation	0.05	0.05	0.352	0.02	0.32	0.05	<0.001	0.13	0.31	0.04	<0.001	0.12	0.14	0.04	0.001	0.06
Women																
Word recall																
Mother's education → Word recall	0.47	0.12	<0.001	0.08	0.27	0.08	0.002	0.05	0.05	0.10	0.587	0.01	0.09	0.09	0.281	0.02
Childhood amenities → Word recall	-0.07	0.05	0.209	-0.03	0.28	0.05	<0.001	0.11	0.05	0.04	0.164	0.02	-0.12	0.05	0.024	-0.04
Education → Word recall	1.04	0.08	<0.001	0.33	0.82	0.07	<0.001	0.21	1.15	0.07	<0.001	0.31	1.23	0.06	<0.001	0.37
Assets → Word recall	0.06	0.04	0.119	0.03	0.23	0.03	<0.001	0.11	0.15	0.03	<0.001	0.08	0.12	0.03	<0.001	0.07
Verbal fluency																
Mother's education → Verbal fluency	0.79	0.22	<0.001	0.07	0.53	0.14	<0.001	0.07	0.77	0.15	<0.001	0.09	0.07	0.15	0.651	0.01
Childhood amenities → Verbal fluency	-0.16	0.10	0.104	-0.03	0.00	0.07	0.983	0.00	0.05	0.06	0.384	0.02	-0.07	0.09	0.445	-0.01
Education → Verbal fluency	2.13	0.14	<0.001	0.37	1.40	0.13	<0.001	0.22	1.62	0.11	<0.001	0.30	1.91	0.11	<0.001	0.35
Assets → Verbal fluency	0.04	0.07	0.499	0.01	0.39	0.06	<0.001	0.12	0.05	0.05	0.340	0.02	0.03	0.05	0.530	0.01
Letter cancellation																
Mother's education → Letter cancellation	0.32	0.17	0.050	0.04	-0.15	0.11	0.175	-0.02	0.44	0.15	0.004	0.05	-0.08	0.12	0.480	-0.01
Childhood amenities → Letter cancellation	0.06	0.07	0.402	0.02	0.20	0.06	0.001	0.06	0.09	0.06	0.147	0.03	0.01	0.07	0.928	0.00
Education → Letter cancellation	0.67	0.10	<0.001	0.16	0.78	0.10	<0.001	0.16	1.01	0.11	<0.001	0.20	1.35	0.08	<0.001	0.32
Assets → Letter cancellation	0.07	0.05	0.158	0.03	0.31	0.05	<0.001	0.12	0.19	0.05	<0.001	0.07	0.16	0.04	<0.001	0.07

b=unstandardized regression coefficient; SE=standard error; Std=standardized regression coefficient

Model fit indices: Word recall: χ^2 (3) =4.561; RMSEA=0.012; CFI=1.000; TLI=0.996; Verbal fluency: χ^2 (3) =4.308, RMSEA=0.011; CFI=1.000; TLI=0.996; Letter cancellation: χ^2 (3) =3.577; RMSEA=0.007; CFI=1.000; TLI=0.998

Because the models were just-identified some statistically insignificant structural paths, which were not of primary interest, were constrained to zero in all models in order to estimate model fit.

4.3. Alcohol consumption and cognitive function

This section presents the results of analysis on alcohol consumption and mid to late life cognitive function. Results from pooled regression analyses of alcohol consumption indices and cognitive function are presented in tables as well as graphically so that the shape of the associations can be more readily inspected by the reader.

4.3.1. Descriptive results

The total number of participants with complete data on all variables used in analyses on alcohol indices and cognitive function was 27,026. Data on alcohol type, based on measures of weekly intake of wine, beer and spirits, were available for 26,808 participants. Participants with missing data for cognitive function had higher mean total alcohol intake ($p<0.001$), were more likely to binge drink ($p<0.001$) or to be non-drinkers ($p<0.001$), to be younger ($p<0.001$), male ($p<0.001$), had lower educational attainment ($p<0.001$), owned fewer assets ($p<0.001$) and were more likely to smoke ($p<0.001$) than those participants, who had cognitive function data.

Summary statistics and frequency distributions of the study variables are presented in Table 4.9. All drinking indices were significantly higher in men than in women. Almost one third of Novosibirsk and Kaunas men were binge drinkers, compared to 16% of Czech and 10% of Polish men. In contrast, binge drinking was rare in women. The proportion of women binge

Table 4.9. Descriptive characteristics of study sample for alcohol consumption and cognitive function (n=27,026)

	Men				Women			
	Czech towns (n=2,565)	**Novosibirsk (n=3,063)**	**Krakow (n=3,706)**	**Kaunas (n=3,101)**	**Czech towns (n=3,005)**	**Novosibirsk (n=3,899)**	**Krakow (n=3,920)**	**Kaunas (n=3,767)**
Word recall	21.8 (3.6)	20.3 (4.7)	19.9 (4.2)	20.9 (4.1)	23.3 (3.5)	21.5 (4.4)	21.1 (4.2)	22.6 (3.8)
Delayed recall	7.2 (1.8)	6.7 (2.2)	6.8 (1.9)	7.3 (1.9)	7.9 (1.7)	7.4 (2.1)	7.3 (1.9)	8.0 (1.7)
Verbal fluency	23.8 (6.8)	19.1 (7.2)	21.1 (6.4)	21.5 (6.1)	23.7 (6.3)	18.7 (6.9)	21.0 (6.3)	21.4 (6.1)
Letter cancellation	17.4 (4.7)	16.5 (5.1)	17.5 (5.7)	15.5 (4.6)	18.5 (4.6)	17.9 (5.4)	18.4 (5.9)	16.8 (4.8)
Global cognition	0.0 (0.7)	0.0 (0.8)	0.0 (0.8)	0.0 (0.8)	0.0 (0.7)	0.0 (0.8)	0.0 (0.8)	0.0 (0.8)
Drinking frequency, (%)								
Never	6.7	13.0	18.0	5.3	18.2	17.8	36.5	7.4
<1 /month	11.9	13.3	15.7	14.0	26.3	48.3	28.8	35.3
1-3 /month	17.7	29.7	23.6	34.2	26.6	27.3	20.1	43.2
1-4 /week	32.9	35.5	30.4	35.7	22.1	6.2	12.8	12.5
5+ /week	30.8	8.5	12.3	10.9	6.8	0.4	1.9	1.7
Alcohol intake, (%)								
Non-drinker	6.7	13.0	18.0	5.3	18.2	17.8	36.5	7.4
<5/10 g per day	44.3	51.8	55.3	62.5	52.0	74.2	48.3	76.7
5-20/10-40 g per day	39.4	27.4	22.8	28.4	22.1	7.0	13.1	13.9
>20/40 g per day	9.6	7.8	3.8	3.8	7.7	1.0	2.1	2.1
Alcohol intake (L) in past year	6.5 (7.9)	5.3 (7.7)	3.9 (6.2)	4.1 (5.6)	2.0 (3.7)	0.7 (1.7)	1.1 (2.2)	1.0 (1.7)
Binge drinking, (%)								
Non-drinker	6.7	13.0	18.0	5.3	18.2	17.8	36.5	7.4
Non-binge drinker	77.2	55.6	71.7	68.6	73.6	75.1	59.7	83.4
Binge drinker	16.1	31.4	10.2	26.2	8.2	7.1	3.8	9.3
Alcohol type (drinkers only)								
Wine, (%)	5.5	3.9	5.0	5.2	21.5	7.0	16.6	16.8
Beer, (%)	51.5	14.7	33.3	19.0	23.1	5.3	10.6	6.2
Spirits, (%)	3.9	24.7	14.3	25.4	6.0	5.9	8.5	22.4
Quantity per occasion (g)	38.7 (21.0)	56.5 (25.6)	37.2 (20.7)	46.4 (22.6)	29.7 (12.7)	31.7 (14.3)	28.6 (10.6)	32.0 (13.9)
Quantity per occasion, (%)	6.7	13.0	18.0	5.3				
Non-drinker	31.0	16.3	36.3	17.5	18.2	17.8	36.5	7.4
<25 g	36.3	11.7	25.8	33.9	56.4	62.5	49.9	60.4
26-40 g	20.6	44.2	14.8	32.1	18.1	3.9	8.6	16.6
41-60/80 g	5.4	14.9	5.1	11.3	3.1	8.7	2.7	9.8
>60/80 g	6.7	13.0	18.0	5.3	4.3	7.2	2.3	5.8
Age	60.4 (6.4)	59.9 (6.4)	60.5 (5.5)	60.5 (7.6)	59.6 (6.4)	59.7 (6.4)	59.9 (5.7)	60.3 (7.6)
Education, (%)								
Primary	4.8	11.2	9.1	12.9	16.6	9.9	13.6	11.0
Secondary	75.1	55.4	58.9	53.0	72.6	63.1	59.0	56.4
University	20.1	33.5	32.0	34.1	10.8	27.0	27.4	32.6
Household assets	7.0 (1.9)	5.6 (2.1)	6.6 (2.1)	7.0 (2.0)	6.5 (1.9)	5.2 (2.1)	6.0 (2.1)	6.3 (2.0)
Self-rated health	2.6 (0.7)	3.0 (0.6)	2.6 (0.8)	2.8 (0.7)	2.6 (0.8)	3.2 (0.6)	2.8 (0.8)	3.0 (0.7)
Self-reported medical conditions								
Myocardial infarction, (%)	7.5	11.0	11.9	10.2	2.3	4.7	4.9	5.8
Ischemic heart disease /Angina, (%)	9.8	18.1	19.0	7.3	6.5	17.7	19.2	12.1
Hypertension, (%)	50.3	53.4	56.9	58.6	46.7	70.8	56.9	59.1
Stroke, (%)	3.6	4.9	2.3	4.5	2.6	4.7	1.8	3.7
Diabetes, (%)	14.0	4.5	14.0	6.8	9.8	7.2	1 0.8	8.0

Figures are means with standard deviations in parentheses or proportions, as appropriate.

drinkers ranged from 3.8% in Krakow to 9.3% in Kaunas. Heavy drinkers (>20/40 g per day in women/men) accounted for 6.0% of all men and 3.0% of all women. In the sample as a whole, 14.8% of men and 2.5% of women were frequent drinkers drinking daily or almost daily. Both heavy and frequent drinking was most common in Czech participants. Czech

Table 4.10. Characteristics of study population grouped by alcohol intake

	Alcohol intake										
	Non-drinker		Light		Moderate		Heavy		Total		P-value
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	
Men											
Total alcohol intake (l)	0.0	(0.0)	1.3	(1.0)	7.5	(2.6)	24.8	(10.7)	4.1	(6.7)	<0.001
Word recall	19.1	(4.5)	20.6	(4.2)	21.2	(4.1)	21.1	(4.2)	20.6	(4.3)	<0.001
Verbal fluency	19.0	(6.8)	21.1	(6.6)	22.3	(6.9)	21.4	(6.8)	21.3	(6.8)	<0.001
Letter search	15.9	(5.6)	16.7	(5.2)	17.1	(4.9)	16.5	(5.0)	16.7	(5.2)	<0.001
Delayed recall	6.5	(2.0)	7.0	(1.9)	7.2	(1.9)	7.1	(2.1)	7.0	(2.0)	<0.001
Global cognition	-0.2	(0.8)	0.0	(0.7)	0.1	(0.7)	0.0	(0.8)	0.0	(0.8)	<0.001
Age	61.5	(6.1)	60.8	(6.5)	59.4	(6.5)	58.0	(6.4)	60.3	(6.5)	<0.001
Education, (%)											<0.001
Primary or less	14.4		9.8		7.9		7.9		9.7		
Secondary	63.2		57.6		60.7		71.0		59.9		
University	22.3		32.6		31.4		21.1		30.4		
Household assets	5.9	(2.1)	6.5	(2.1)	6.9	(2.1)	6.4	(2.1)	6.5	(2.1)	<0.001
Smoking status, (%)											<0.001
Never smoked	29.3		35.1		27.0		14.5		30.9		
Current smoker	31.5		29.8		38.2		50.9		33.7		
Former smoker	39.2		35.2		34.8		34.5		35.5		
Self-rated health	3.0	(0.8)	3.2	(0.7)	3.4	(0.7)	3.2	(0.7)			<0.001
Medical history											
MI, (%)	16.1		11.0		7.7		6.3		10.3		<0.001
Angina/ISH, (%)	21.8		14.9		10.1		9.1		14.0		<0.001
Stroke, (%)	5.9		4.0		2.7		2.3		3.7		<0.001
High blood pressure, (%)	55.9		55.8		53.6		54.3		55.1		<0.001
Diabetes, (%)	14.1		10.1		8.1		7.7		9.9		<0.001
N	**1401**		**6713**		**3577**		**744**		**12366**		
Women											
Total alcohol intake (l)	0.0	(0.0)	0.4	(0.4)	2.9	(1.3)	10.1	(6.4)	0.9	(2.2)	<0.001
Word recall	20.2	(4.3)	22.3	(4.0)	23.3	(3.5)	23.6	(3.5)	22.1	(4.1)	<0.001
Verbal fluency	18.9	(6.4)	21.2	(6.6)	23.1	(6.4)	24.0	(6.6)	21.0	(6.6)	<0.001
Letter search	16.8	(5.6)	18.0	(5.2)	18.9	(5.0)	18.6	(4.8)	17.9	(5.3)	<0.001
Delayed recall	6.9	(2.0)	7.7	(1.8)	8.1	(1.7)	8.2	(1.8)	7.6	(1.9)	<0.001
Global cognition	-0.3	(0.8)	0.1	(0.7)	0.2	(0.7)	0.2	(0.7)	0.0	(0.8)	<0.001
Age	62.3	(5.6)	59.7	(6.6)	57.6	(6.3)	57.6	(6.7)	59.9	(6.6)	<0.001
Education, (%)											<0.001
Primary	20.9		10.8		8.6		9.7		12.5		
Secondary	62.0		63.0		59.7		58.9		62.2		
University	17.1		26.1		31.8		31.3		25.2		
Household assets	5.3	(2.0)	6.0	(2.0)	6.8	(2.0)	6.9	(2.1)	6.0	(2.1)	<0.001
Smoking status, (%)											<0.001
Never smoked	70.9		73.5		56.3		47.6		69.8		
Current smoker	14.7		13.9		23.1		28.5		15.7		
Former smoker	14.5		12.7		20.6		23.9				
Self-rated health	2.9	(0.8)	3.1	(0.7)	3.3	(0.7)	3.4	(0.8)	3.1	(0.7)	<0.001
Medical history											
MI, (%)	7.4		4.1		2.7		2.1		4.5		<0.001
Angina/ISH, (%)	23.5		13.3		7.3		6.7		14.3		<0.001
Stroke, (%)	5.9		2.7		1.5		3.2		3.2		<0.001
High blood pressure, (%)	66.2		60.2		46.9		42.0		59.1		<0.001
Diabetes, (%)	14.3		8.1		5.3		5.3		8.9		<0.001
N	**2947**		**9240**		**1973**		**431**		**14533**		

Figures are means with standard deviations in parentheses or proportions, as appropriate.
P-values are from t-test, ANOVA or chi-square test, as appropriate.

men had the highest mean alcohol intake in the past year (6.5 litres), followed by men in Novosibirsk (5.3 litres). Similarly, Czech women also had the highest mean alcohol intake (2 litres) but Russian women had the lowest (0.7 litre). The highest average amount of ethanol per single occasion (56.5 g) was consumed by men in Novosibirsk, followed by men in Kaunas. Corresponding quantities for Czech and Polish men were 38.7 and 37.2 g, respectively. In women, average quantity consumed per occasion was relatively similar across centres. Half of Czech and one third of Krakow men typically drank beer, whereas one quarter of Novosibirsk and Kaunas men drank mainly spirits. Women were more likely than men to drink wine and less likely to consume predominantly one type of alcohol.

Unadjusted characteristics of participants stratified by alcohol intake for the pooled sample are shown in Table 4.10. Among men, heavy drinkers had lower unadjusted mean cognitive scores for several tests compared to moderate drinkers (all pairwise comparisons for fluency, search speed and global cognition $p<0.05$, Bonferroni adjusted) and generally similar scores to light drinkers. Cognitive test scores were consistently lower in non-drinkers than in drinkers. In women, cognitive scores increased with increasing alcohol intake on all tests (tests for trend $p<0.001$). Alcohol consumption decreased with age in both genders (tests for trend $p<0.001$) and non-drinkers were older than drinkers. Among men, non-drinkers and heavy drinkers were significantly less likely to have university education than light or moderate drinkers. In contrast, in women a higher proportion of both heavy and moderate drinkers had university education compared to light drinkers or abstainers. Compared to drinkers, non-drinkers were also more likely to have low education. A similar pattern was observed for current material circumstances, measured by household assets. One half of heavy male drinkers were current smokers compared to the sample average of one third. Among women heavy drinkers were also more likely to smoke. Non-drinkers had a higher

prevalence of medical conditions than drinkers, perhaps partly as a result of being older and because a significant proportion, especially among men, are probably former drinkers who quit drinking because of ill health; it was not possible to distinguish between former drinkers and lifelong abstainers in centres other than Novosibirsk.

4.3.2. Regression analysis

There was significant heterogeneity in the associations between alcohol and cognitive function (except letter cancellation) between study centres, which was driven entirely by the inclusion of non-drinkers in the analysis. Compared to light drinkers, non-drinkers had significantly lower cognitive scores in Czech and Polish samples but not in Russian and Lithuanian samples. Interactions between alcohol indices and centre were not significant in analyses excluding non-drinkers. The pooled analyses include non-drinkers and the results on non-drinkers should be interpreted with caution; the interaction did not affect results among drinkers, which are the main focus of these analyses.

Results from sequentially adjusted regression models for cognitive function and total alcohol intake are shown in Table 4.11. In age-adjusted models male heavy drinkers (>40 g per day) had worse performance on all cognitive tests, compared to the reference group. This association was significantly attenuated after adjusting for socioeconomic confounders (Model 2) but only slightly, if at all, after additionally adjusting for smoking (Model 3). In these models men drinking more than 40 g per day had non-significantly lower cognitive scores for immediate recall and verbal fluency, significantly lower letter search scores

Table 4.11. Regression estimates for cognitive function and total alcohol intake

	Model 1: Age		Model 2: Education, assets		Model 3: Smoking		Model 4: Health	
	b	SE	b	SE	b	SE	b	SE
Men (n=12,435)								
Word recall								
Alcohol intake (per day)								
Non-drinker	-0.23***	(0.03)	-0.15***	(0.03)	-0.15***	(0.03)	-0.13***	(0.03)
<10 g	0.00		0.00		0.00		0.00	
10-40 g	0.05**	(0.02)	0.04*	(0.02)	0.04*	(0.02)	0.03	(0.02)
>40 g /day	-0.09*	(0.04)	-0.03	(0.03)	-0.03	(0.03)	-0.04	(0.03)
Verbal fluency								
Alcohol intake (per day)								
Non-drinker	-0.24***	(0.03)	-0.16***	(0.03)	-0.17***	(0.03)	-0.15***	(0.03)
<10 g	0.00		0.00		0.00		0.00	
10-40 g	0.07***	(0.02)	0.06**	(0.02)	0.06**	(0.02)	0.05**	(0.02)
>40 g	-0.11**	(0.04)	-0.06	(0.04)	-0.06	(0.04)	-0.06	(0.04)
Letter cancellation								
Alcohol intake (per day)								
Non-drinker	-0.19***	(0.03)	-0.10***	(0.03)	-0.10***	(0.03)	-0.08**	(0.03)
<10 g	0.00		0.00		0.00		0.00	
10-40 g	0.01	(0.02)	-0.01	(0.02)	-0.00	(0.02)	-0.01	(0.02)
>40 g	-0.17***	(0.04)	-0.11**	(0.04)	-0.10**	(0.04)	-0.11**	(0.04)
Delayed recall								
Alcohol intake (per day)								
Non-drinker	-0.17***	(0.03)	-0.10***	(0.03)	-0.10***	(0.03)	-0.08**	(0.03)
<10 g	0.00		0.00		0.00		0.00	
10-40 g	0.03	(0.02)	0.02	(0.02)	0.02	(0.02)	0.01	(0.02)
>40 g	-0.13***	(0.04)	-0.08*	(0.04)	-0.08*	(0.04)	-0.09*	(0.04)
Women (n=14,591)								
Word recall								
Alcohol intake (per day)								
Non-drinker	-0.28***	(0.02)	-0.20***	(0.02)	-0.20***	(0.02)	-0.18***	(0.02)
<5 g	0.00		0.00		0.00		0.00	
5-20 g	0.09***	(0.02)	0.03	(0.02)	0.03	(0.02)	0.02	(0.02)
>20 g	0.12**	(0.05)	0.05	(0.04)	0.05	(0.04)	0.04	(0.04)
Verbal fluency								
Alcohol intake (per day)								
Non-drinker	-0.25***	(0.02)	-0.18***	(0.02)	-0.18***	(0.02)	-0.16***	(0.02)
<5 g	0.00		0.00		0.00		0.00	
5-20 g	0.09***	(0.02)	0.04	(0.02)	0.03	(0.02)	0.03	(0.02)
>20 g	0.14**	(0.05)	0.07	(0.04)	0.06	(0.04)	0.06	(0.04)
Letter cancellation								
Alcohol intake (per day)								
Non-drinker	-0.21***	(0.02)	-0.15***	(0.02)	-0.15***	(0.02)	-0.12***	(0.02)
<5 g	0.00		0.00		0.00		0.00	
5-20 g	0.06*	(0.02)	0.02	(0.02)	0.02	(0.02)	0.01	(0.02)
>20 g	-0.02	(0.05)	-0.08	(0.05)	-0.08	(0.05)	-0.08	(0.05)
Delayed recall								
Alcohol intake (per day)								
Non-drinker	-0.21***	(0.02)	-0.15***	(0.02)	-0.15***	(0.02)	-0.13***	(0.02)
<5 g	0.00		0.00		0.00		0.00	
5-20 g	0.09***	(0.02)	0.05*	(0.02)	0.05*	(0.02)	0.04	(0.02)
>20 g	0.12**	(0.05)	0.06	(0.05)	0.06	(0.05)	0.06	(0.05)

b=regression coefficient; SE=standard error

Model 1: Age-adjusted.

Model 2: Additionally adjusted for education and assets.

Model 3: Additionally adjusted for smoking.

Model 4: Additionally adjusted for self-rated health and self-reported medical conditions.

All models are also adjusted for measurement wave and centre.

Reference group is light drinker (<10 g daily in men and <5 g daily in women).

* p <0.05, ** p <0.01, *** p <0.001

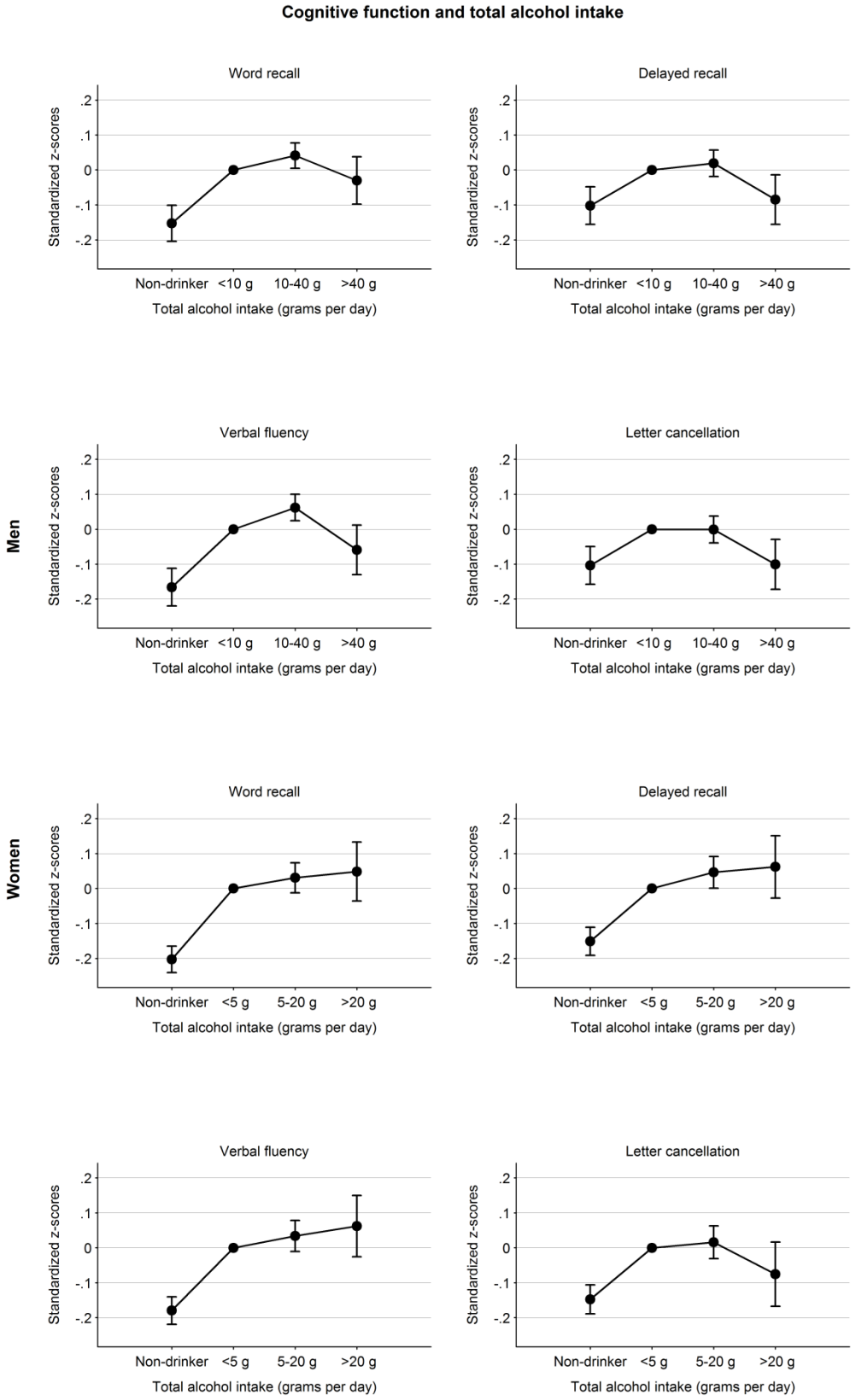

Figure 4.2. Adjusted regression coefficients (with 95% confidence intervals) for association of cognitive function with total alcohol intake
Reference group is daily alcohol intake of <5/10 g in women and men, respectively.

($p<0.01$) and marginally worse delayed recall scores ($p<0.05$), compared to men drinking less than 10 g a day. In contrast, moderate male drinkers (10-40 g per day) had significantly better cognitive scores for word recall and verbal fluency (both $p<0.001$) compared to light drinkers (<10 g per day). In women, total alcohol intake was generally not significantly associated with cognition after adjusting for socioeconomic confounders and smoking, lower scores in abstainers exempt.

Adjusted regression coefficients with 95% CIs (from Model 3) are shown graphically in Figure 4.2. As seen in the figure, in men the association between total alcohol intake and cognitive performance consistently showed an inverted U-shaped pattern, indicating worsening of cognitive scores in abstainers and heavy drinkers. In women, however, this pattern was only apparent for letter cancellation. In women there was a near-linear improvement in cognitive scores among drinkers for the verbal measures.

Further adjustments for health measures had little impact on the associations between alcohol intake and cognitive performance (Model 4). Regression coefficients for heavy male drinkers generally increased slightly after adjustments for health measures.

Table 4.12. Regression estimates for cognitive function and drinking frequency

	Model 1: Age		Model 2: Education, assets		Model 3: Smoking		Model 4: Health	
	b	SE	b	SE	b	SE	b	SE
Men (n=12,435)								
Word recall								
Drinking frequency								
Never	-0.20***	(0.03)	-0.14***	(0.03)	-0.14***	(0.03)	-0.12***	(0.03)
<1 /month	0.00		0.00		0.00		0.00	
1-3 /month	0.04	(0.03)	0.01	(0.03)	0.01	(0.03)	0.00	(0.03)
3-4 /week	0.07*	(0.03)	0.03	(0.03)	0.04	(0.03)	0.01	(0.03)
5+ /week	0.07*	(0.03)	0.06	(0.03)	0.06	(0.03)	0.03	(0.03)
Verbal fluency								
Drinking frequency								
Never	-0.20***	(0.03)	-0.15***	(0.03)	-0.15***	(0.03)	-0.14***	(0.03)
<1 /month	0.00		0.00		0.00		0.00	
1-3 /month	0.03	(0.03)	0.00	(0.03)	0.00	(0.03)	-0.00	(0.03)
3-4 /week	0.09***	(0.03)	0.06*	(0.03)	0.06*	(0.03)	0.05	(0.03)
5+ /week	0.08*	(0.03)	0.06	(0.03)	0.06	(0.03)	0.05	(0.03)
Letter cancellation								
Drinking frequency								
Never	-0.14***	(0.03)	-0.08*	(0.03)	-0.08*	(0.03)	-0.07*	(0.03)
<1 /month	0.00		0.00		0.00		0.00	
1-3 /month	0.05	(0.03)	0.03	(0.03)	0.03	(0.03)	0.02	(0.03)
3-4 /week	0.04	(0.03)	0.00	(0.03)	0.01	(0.03)	-0.01	(0.03)
5+ /week	0.02	(0.03)	0.01	(0.03)	0.02	(0.03)	-0.00	(0.03)
Delayed recall								
Drinking frequency								
Never	-0.16***	(0.03)	-0.11***	(0.03)	-0.11***	(0.03)	-0.10**	(0.03)
<1 /month	0.00		0.00		0.00		0.00	
1-3 /month	-0.00	(0.03)	-0.02	(0.03)	-0.02	(0.03)	-0.03	(0.03)
3-4 /week	0.03	(0.03)	0.01	(0.03)	0.00	(0.03)	-0.02	(0.03)
5+ /week	0.00	(0.03)	-0.01	(0.03)	-0.01	(0.03)	-0.03	(0.03)
Women (n=14,591)								
Word recall								
Drinking frequency								
Never	-0.22***	(0.02)	-0.17***	(0.02)	-0.17***	(0.02)	-0.15***	(0.02)
<1 /month	0.00		0.00		0.00		0.00	
1-3 /month	0.15***	(0.02)	0.09***	(0.02)	0.09***	(0.02)	0.08***	(0.02)
3-4 /week	0.15***	(0.03)	0.07**	(0.02)	0.07**	(0.02)	0.06*	(0.02)
5+ /week	0.24***	(0.05)	0.13**	(0.05)	0.12**	(0.05)	0.12*	(0.05)
Verbal fluency								
Drinking frequency								
Never	-0.21***	(0.02)	-0.16***	(0.02)	-0.16***	(0.02)	-0.14***	(0.02)
<1 /month	0.00		0.00		0.00		0.00	
1-3 /month	0.11***	(0.02)	0.05**	(0.02)	0.05**	(0.02)	0.04*	(0.02)
3-4 /week	0.14***	(0.03)	0.06*	(0.02)	0.06*	(0.02)	0.05	(0.02)
5+ /week	0.26***	(0.05)	0.14**	(0.05)	0.14**	(0.05)	0.13**	(0.05)
Letter cancellation								
Drinking frequency								
Never	-0.17***	(0.02)	-0.13***	(0.02)	-0.12***	(0.02)	-0.10***	(0.02)
<1 /month	0.00		0.00		0.00		0.00	
1-3 /month	0.10***	(0.02)	0.06**	(0.02)	0.06**	(0.02)	0.05*	(0.02)
3-4 /week	0.10***	(0.03)	0.04	(0.03)	0.04	(0.03)	0.03	(0.03)
5+ /week	0.06	(0.05)	-0.03	(0.05)	-0.03	(0.05)	-0.04	(0.05)
Delayed recall								
Drinking frequency								
Never	-0.17***	(0.02)	-0.13***	(0.02)	-0.12***	(0.02)	-0.11***	(0.02)
<1 /month	0.00		0.00		0.00		0.00	
1-3 /month	0.11***	(0.02)	0.07***	(0.02)	0.07***	(0.02)	0.06**	(0.02)
3-4 /week	0.14***	(0.03)	0.07**	(0.03)	0.07**	(0.03)	0.06*	(0.03)
5+ /week	0.20***	(0.05)	0.11*	(0.05)	0.11*	(0.05)	0.11*	(0.05)

b=regression coefficient; SE=standard error
Model 1: Age-adjusted.
Model 2: Additionally adjusted for education and assets.
Model 3: Additionally adjusted for smoking.
Model 4: Additionally adjusted for self-rated health and self-reported medical conditions.
All models are also adjusted for measurement wave and centre.
Reference group is infrequent drinker (<1 per month).
* p <0.05, ** p <0.01, *** p <0.001

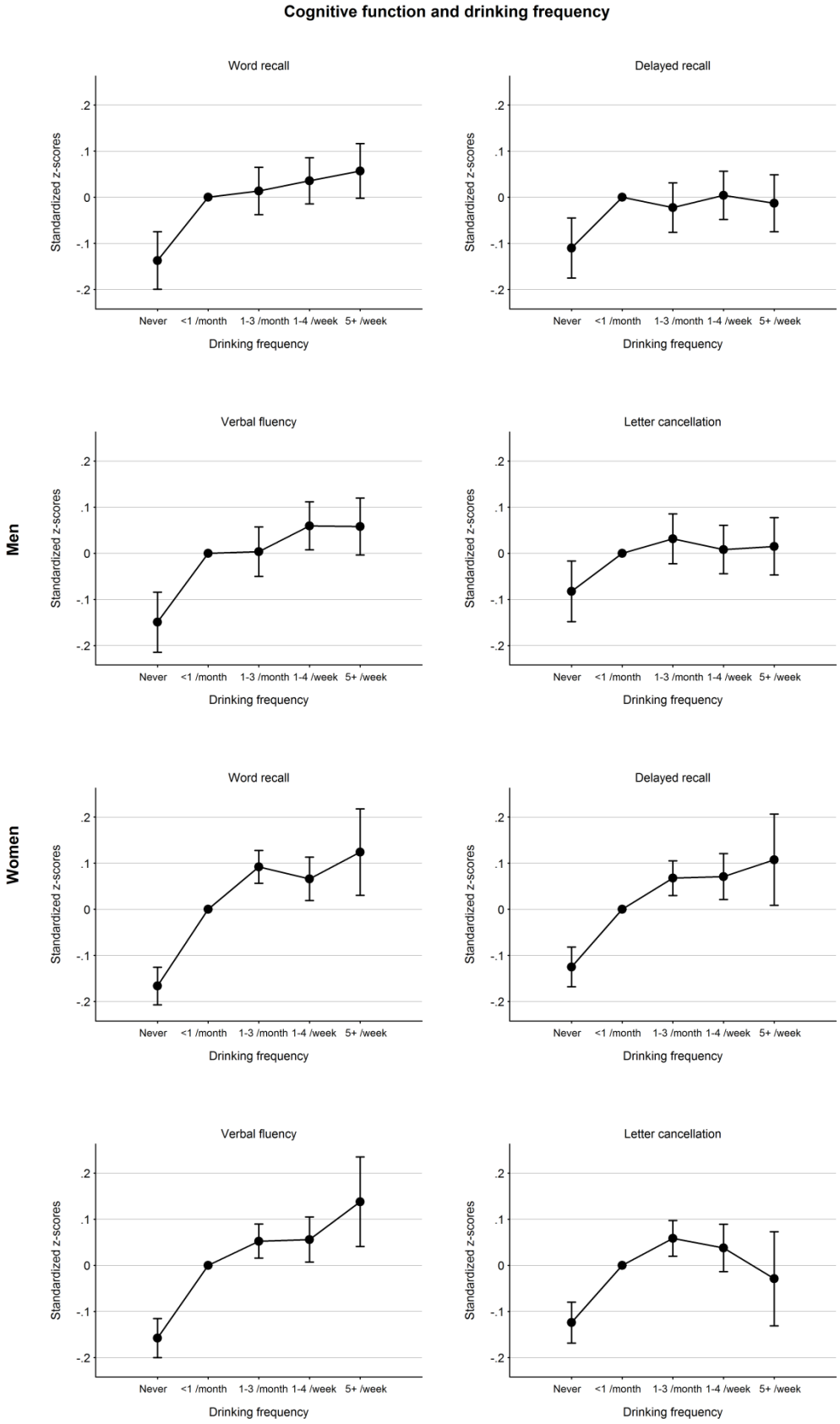

Figure 4.3. Adjusted regression coefficients (with 95% confidence intervals) for association of cognitive function with drinking frequency
Reference group is infrequent drinker (<1 per month).

Results for drinking frequency are shown in Table 4.12. and graphically in Figure 4.3. (results from Model 3). With the exception of lower scores in non-drinkers, drinking frequency was generally not significantly associated with cognitive function in men, after adjusting for socioeconomic confounders and smoking (Model 3). As seen in Figure 4.3., in men there was a slight upward trend with increasing drinking frequency in cognitive scores for word recall and verbal fluency but no similar trend was observed for letter search and delayed recall. In women, however, drinking frequency showed an approximately dose-response association with cognitive performance on all verbal cognitive tests. Higher drinking frequency was significantly associated with better cognition, especially for immediate and delayed recall, although the relationship was substantially weakened after adjusting for socioeconomic confounders (Model 2). The positive associations between drinking frequency and cognitive scores were attenuated only slightly after further adjustments for health measures (Model 4). In contrast, letter cancellation performance showed an inverse U-shaped pattern with non-significantly worse scores among (almost) daily female drinkers, compared to the reference group.

There were significant interactions between age and drinking frequency for immediate ($p<0.001$) and delayed recall ($p<0.01$) in women and age and total alcohol intake for verbal fluency ($p<0.01$) in men. Post hoc stratified analysis suggested that among older women (aged 54-64, and especially those aged 65+) frequent drinkers (1-3 times monthly or more) had better cognitive scores for immediate and, to a lesser extent, delayed recall than in younger women (aged 45-54). In men younger abstainers had better scores on verbal fluency than older abstainers.

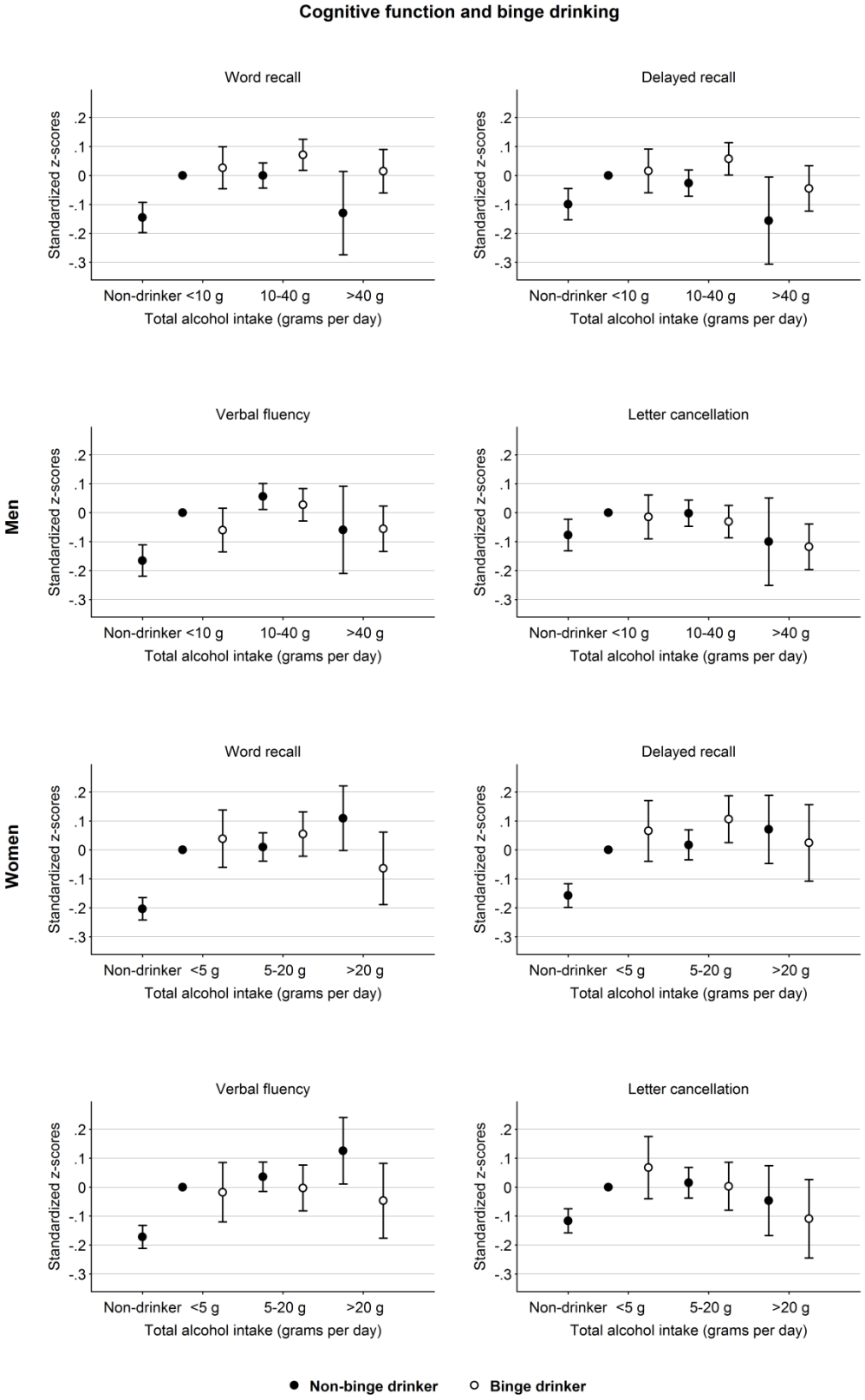

Figure 4.4. Adjusted regression coefficients (with 95% confidence intervals) for association of cognitive function with alcohol intake stratified by binge drinking
Reference group is light (<5/10 g daily) non-binge drinker.

Figure 4.4. shows results of analysis of drinking volume stratified by binge drinking. The estimates are adjusted for age, socioeconomic confounders and smoking. Binge drinking was not systematically associated with cognitive scores across levels of alcohol intake; at each intake cognitive scores in binge drinkers were mostly similar to those in non-binge drinkers. This suggests that binge drinking is not independently associated with cognitive performance, after accounting for total alcohol volume. This finding is supported by additional analyses in which binge drinking was not systematically associated with cognitive function after controlling for drinking volume (shown in Appendix VII, pg. 260).

Results for average quantity of alcohol consumed per occasion and cognitive function adjusted for age, socioeconomic confounders and smoking are shown in Figure 4.5. The quantity of alcohol consumed per occasion showed generally weak inverse U-shaped associations with cognitive outcomes in men; worsening of cognitive scores at high mean dosages was not consistent across outcome measures. In women, average quantity consumed per occasion showed an inverse U-shaped association for all verbal cognitive outcomes but not mental speed. Women drinking more than 60 g per occasion had significantly lower scores on verbal fluency ($p<0.01$), compared to women drinking less than 25 g per occasion, after adjusting for relevant confounders. In contrast, women drinking up to 60 g per occasion showed significantly better performance on immediate and delayed recall.

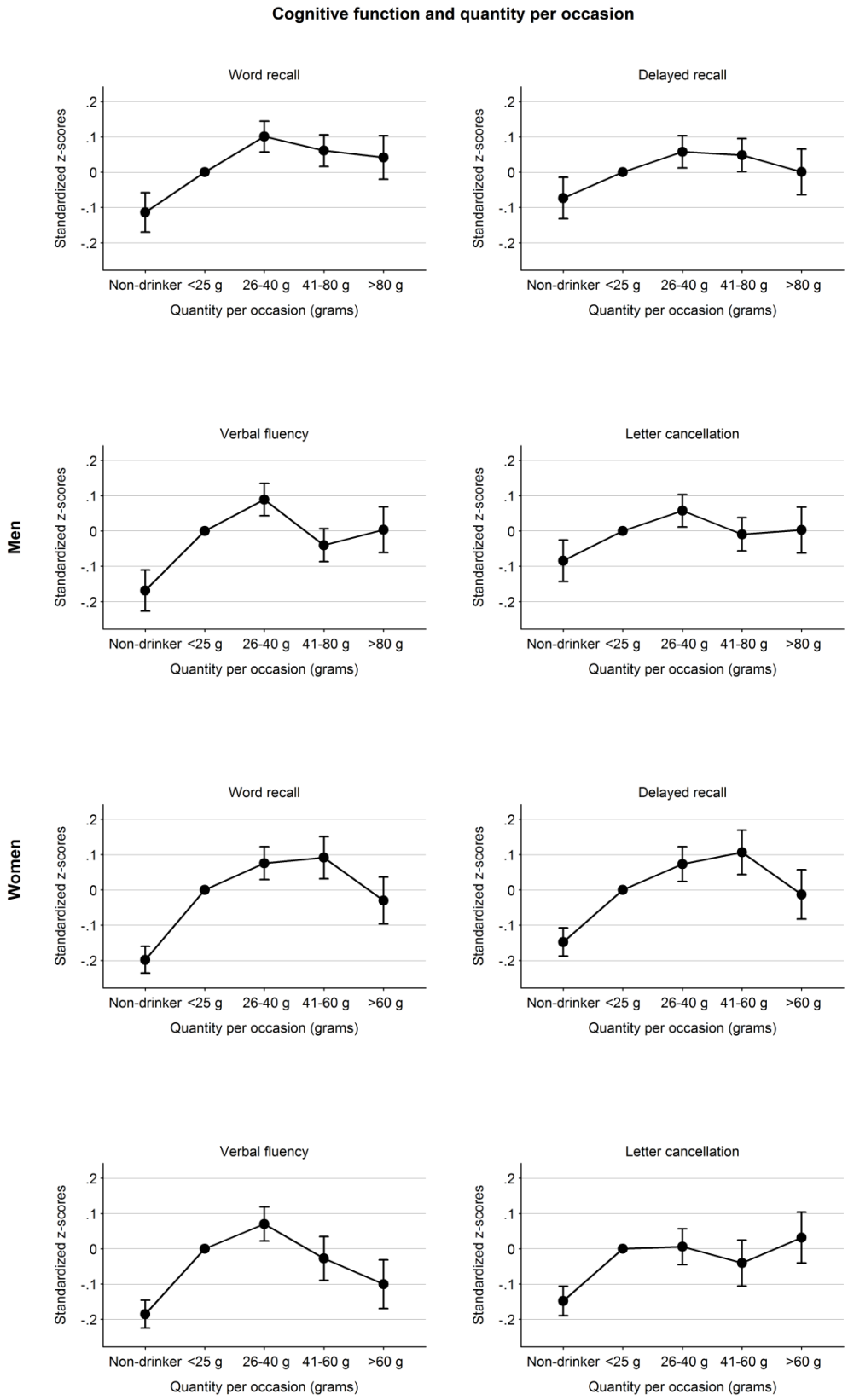

Figure 4.5. Adjusted regression coefficients (with 95% confidence intervals) for association of cognitive function with quantity per occasion
Reference group is average quantity of <25 g of ethanol per occasion.

Finally, Figure 4.6. shows regression estimates and 95% CIs for associations of alcohol consumption measures with global cognition, adjusted for potential confounders (age, socioeconomic variables and smoking). In men, total alcohol intake showed an inverse U-shaped relationship with global cognition with worsening scores among heavier drinkers ($p<0.01$), compared to light drinkers. Frequency, binge drinking and quantity per occasion were not significantly associated with global cognitive scores in male drinkers, although there was a suggestion of worsening of cognitive scores in the heaviest drinking category for binge drinking and quantity per occasion. In women, binge drinking was not associated with global cognition, whereas higher drinking frequencies were associated with significantly better global cognitive scores, compared to infrequent drinking. Moderate female drinkers (5-20 g per day) also had slightly better global scores ($p<0.05$) than light drinkers, whereas global cognitive scores appeared to plateau in heavy drinkers (>20 g per day). In women quantity per occasion followed a weak inverse U-shaped relationship with global cognition, with somewhat better global cognitive scores at medium intakes (21-40 g per occasion) and non-significant worsening of scores at high intakes (>60 g per occasion). For all alcohol indices non-drinkers had significantly lower global cognitive scores than light drinkers (reference group).

In order to examine potential modification effects of drinking pattern, data on drinking frequency and total alcohol intake were combined to distinguish between different types of drinkers. However, this analysis provided few new insights over the conventional measures of frequency, total intake, binge drinking and quantity per occasion. As seen in Table 4.13., occasional heavy alcohol consumption (<2/4 drinks per occasion at least weekly in women/men) was mostly associated with better performance on tests of verbal cognition in both genders in models adjusted for relevant confounders (Model 3). Worsening of cognitive

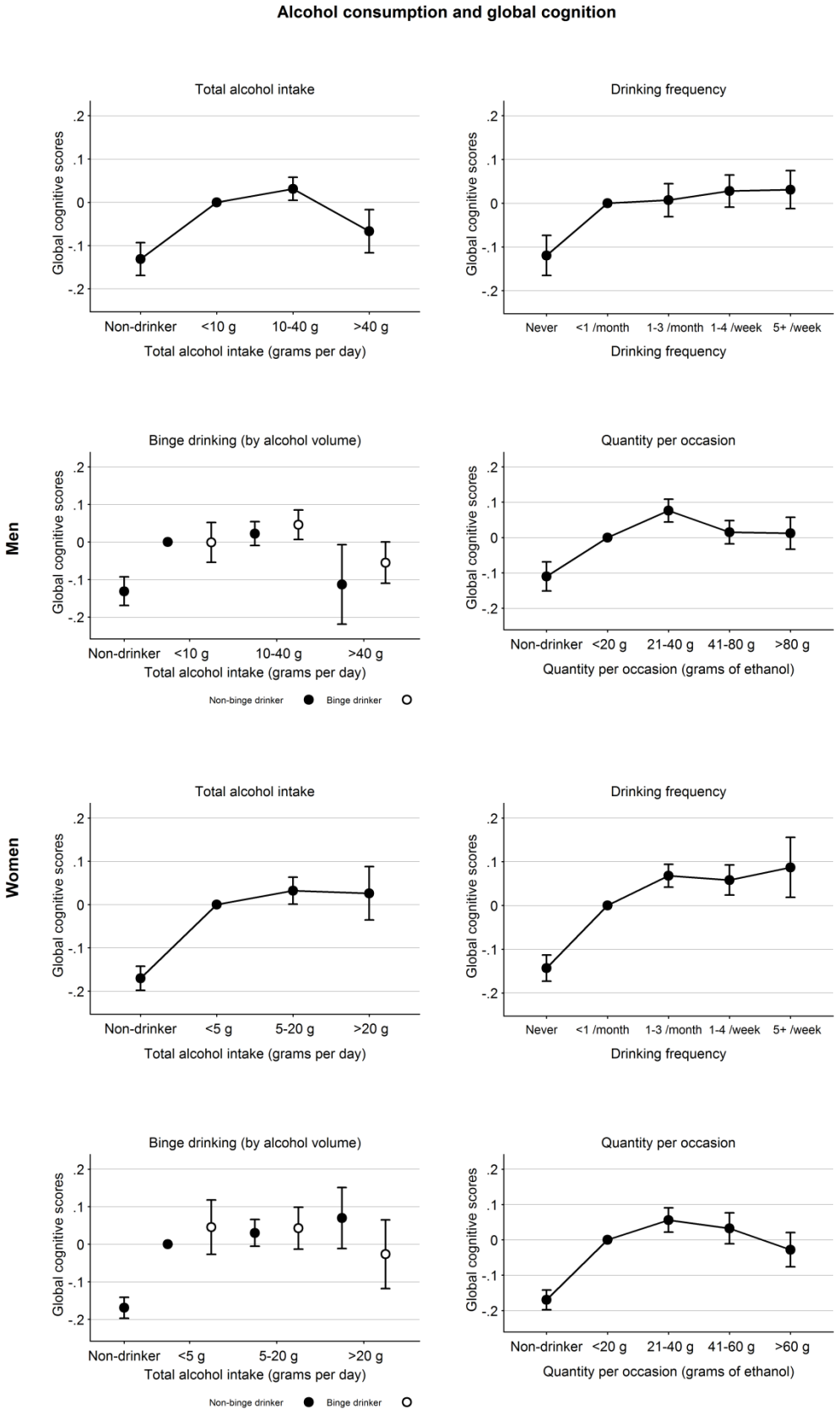

Figure 4.6. Adjusted regression coefficients (with 95% confidence intervals) for associations of global cognition with drinking measures
Reference group is the lowest drinking category for all alcohol indices.

Table 4.13. Regression estimates for cognitive function and drinking pattern

	Model 1: Age		Model 2: Education, assets		Model 3: Smoking		Model 4: Health	
	b	SE	b	SE	b	SE	b	SE
Men (n=12,435)								
Word recall								
Drinking pattern								
Non-drinker	-0.22***	(0.03)	-0.14***	(0.03)	-0.14***	(0.03)	-0.12***	(0.03)
Occasional moderate	0.00		0.00		0.00		0.00	
Regular moderate	-0.01	(0.03)	-0.03	(0.02)	-0.03	(0.02)	-0.04	(0.02)
Occasional heavy	0.08***	(0.02)	0.09***	(0.02)	0.09***	(0.02)	0.07***	(0.02)
Regular heavy	-0.06	(0.04)	-0.00	(0.03)	0.00	(0.04)	-0.02	(0.04)
Verbal fluency								
Drinking pattern								
Non-drinker	-0.22***	(0.03)	-0.14***	(0.03)	-0.14***	(0.03)	-0.13***	(0.03)
Occasional moderate	0.00		0.00		0.00		0.00	
Regular moderate	0.07*	(0.03)	0.05	(0.03)	0.05	(0.03)	0.04	(0.03)
Occasional heavy	0.06**	(0.02)	0.07***	(0.02)	0.07**	(0.02)	0.06*	(0.02)
Regular heavy	-0.03	(0.04)	0.02	(0.04)	0.02	(0.04)	0.01	(0.04)
Letter cancellation								
Drinking pattern								
Non-drinker	-0.18***	(0.03)	-0.09**	(0.03)	-0.09**	(0.03)	-0.08*	(0.03)
Occasional moderate	0.00		0.00		0.00		0.00	
Regular moderate	0.03	(0.03)	0.01	(0.03)	0.01	(0.03)	0.00	(0.03)
Occasional heavy	0.01	(0.02)	0.02	(0.02)	0.03	(0.02)	0.01	(0.02)
Regular heavy	-0.15***	(0.04)	-0.10**	(0.04)	-0.08*	(0.04)	-0.10**	(0.04)
Delayed recall								
Drinking pattern								
Non-drinker	-0.14***	(0.03)	-0.08*	(0.03)	-0.08**	(0.03)	-0.06*	(0.03)
Occasional moderate	0.00		0.00		0.00		0.00	
Regular moderate	-0.01	(0.03)	-0.02	(0.03)	-0.02	(0.03)	-0.03	(0.03)
Occasional heavy	0.09***	(0.02)	0.09***	(0.02)	0.09***	(0.02)	0.07***	(0.02)
Regular heavy	-0.07	(0.04)	-0.03	(0.04)	-0.03	(0.04)	-0.04	(0.04)
Women (n=14,591)								
Word recall								
Drinking pattern								
Non-drinker	-0.27***	(0.02)	-0.19***	(0.02)	-0.19***	(0.02)	-0.17***	(0.02)
Occasional moderate	0.00		0.00		0.00		0.00	
Regular moderate	0.11***	(0.03)	0.05	(0.03)	0.05	(0.03)	0.04	(0.03)
Occasional heavy	0.08***	(0.02)	0.07***	(0.02)	0.07***	(0.02)	0.06**	(0.02)
Regular heavy	-0.04	(0.07)	-0.03	(0.07)	-0.03	(0.07)	-0.04	(0.07)
Verbal fluency								
Drinking pattern								
Non-drinker	-0.26***	(0.02)	-0.18***	(0.02)	-0.18***	(0.02)	-0.16***	(0.02)
Occasional moderate	0.00		0.00		0.00		0.00	
Regular moderate	0.09**	(0.03)	0.03	(0.03)	0.03	(0.03)	0.02	(0.03)
Occasional heavy	0.02	(0.02)	0.01	(0.02)	0.01	(0.02)	-0.00	(0.02)
Regular heavy	0.02	(0.08)	0.03	(0.07)	0.02	(0.07)	0.01	(0.07)
Letter cancellation								
Drinking pattern								
Non-drinker	-0.21***	(0.02)	-0.15***	(0.02)	-0.15***	(0.02)	-0.12***	(0.02)
Occasional moderate	0.00		0.00		0.00		0.00	
Regular moderate	0.05	(0.03)	-0.00	(0.03)	-0.00	(0.03)	-0.01	(0.03)
Occasional heavy	0.01	(0.02)	-0.00	(0.02)	0.00	(0.02)	-0.01	(0.02)
Regular heavy	-0.10	(0.08)	-0.09	(0.08)	-0.09	(0.08)	-0.09	(0.08)
Delayed recall								
Drinking pattern								
Non-drinker	-0.21***	(0.02)	-0.14***	(0.02)	-0.14***	(0.02)	-0.12***	(0.02)
Occasional moderate	0.00		0.00		0.00		0.00	
Regular moderate	0.08**	(0.03)	0.03	(0.03)	0.03	(0.03)	0.03	(0.03)
Occasional heavy	0.08***	(0.02)	0.07***	(0.02)	0.07***	(0.02)	0.06**	(0.02)
Regular heavy	0.03	(0.08)	0.04	(0.07)	0.04	(0.07)	0.03	(0.07)

b=regression coefficient; SE=standard error

Model 1: Age-adjusted.

Model 2: Additionally adjusted for education and assets.

Model 3: Additionally adjusted for smoking.

Model 4: Additionally adjusted for self-rated health and self-reported medical conditions.

All models also adjusted for measurement wave and centre.

Reference group is occasional moderate drinking pattern.

* p <0.05, ** p <0.01, *** p <0.001

scores was seen only in regular heavy male drinkers (≥4 drinks per occasion at least weekly) and for letter cancellation and memory also for regular heavy female drinkers (≥2 drinks per occasion at least weekly). However, with the exception of mental speed test in men, these associations were not statistically significant.

Table 4.14. Adjusted regression estimates for standardized cognitive z-scores and type of alcohol in drinkers

	Czech towns		Novosibirsk		Krakow		Kaunas		All centres		
	b	**SE**	**b**	**SE**	**b**	**SE**	**b**	**SE**	**b**	**SE**	**p-value**
Men											
Wine											
Word recall	0.11	(0.08)	0.01	(0.08)	0.13	(0.07)	0.07	(0.07)	0.07	(0.04)	
Verbal fluency	0.13	(0.08)	-0.00	(0.09)	0.22**	(0.07)	-0.01	(0.08)	0.08*	(0.04)	
Letter search	-0.07	(0.08)	-0.15	(0.09)	0.19*	(0.08)	0.10	(0.07)	0.03	(0.04)	0.019
Delayed recall	0.00	(0.08)	0.08	(0.08)	0.09	(0.08)	0.03	(0.08)	0.04	(0.04)	
Global cognition	0.04	(0.05)	-0.02	(0.06)	0.15**	(0.05)	0.05	(0.05)	0.05*	(0.03)	
Beer											
Word recall	-0.06	(0.04)	0.07	(0.05)	-0.03	(0.03)	0.06	(0.04)	0.00	(0.02)	0.015
Verbal fluency	-0.03	(0.04)	0.05	(0.05)	-0.08*	(0.04)	0.03	(0.04)	-0.01	(0.02)	0.020
Letter search	0.01	(0.04)	0.03	(0.05)	0.03	(0.04)	0.08	(0.04)	0.04	(0.02)	
Delayed recall	-0.06	(0.04)	0.06	(0.05)	0.01	(0.04)	0.08	(0.04)	0.01	(0.02)	0.030
Global cognition	-0.03	(0.03)	0.05	(0.03)	-0.02	(0.03)	0.06*	(0.03)	0.01	(0.01)	0.006
Spirits											
Word recall	-0.14	(0.11)	-0.06	(0.04)	-0.04	(0.05)	0.01	(0.04)	-0.05*	(0.02)	
Verbal fluency	-0.04	(0.11)	0.01	(0.04)	-0.07	(0.05)	0.05	(0.04)	-0.00	(0.02)	
Letter search	-0.10	(0.11)	-0.04	(0.04)	0.00	(0.05)	-0.08*	(0.04)	-0.04	(0.02)	
Delayed recall	-0.10	(0.11)	-0.03	(0.04)	-0.04	(0.05)	0.03	(0.04)	-0.00	(0.02)	
Global cognition	-0.10	(0.08)	-0.03	(0.03)	-0.04	(0.03)	0.00	(0.03)	-0.02	(0.02)	
N	**2352**		**2665**		**2985**		**2938**		**10940**		
Women											
Wine											
Word recall	0.09*	(0.04)	0.06	(0.06)	-0.04	(0.04)	0.03	(0.04)	0.04	(0.02)	
Verbal fluency	0.01	(0.05)	0.10	(0.06)	-0.05	(0.05)	0.08	(0.04)	0.02	(0.02)	
Letter search	0.02	(0.05)	0.09	(0.07)	-0.06	(0.05)	0.01	(0.04)	0.01	(0.02)	
Delayed recall	0.04	(0.05)	0.07	(0.06)	0.02	(0.05)	0.03	(0.04)	0.05*	(0.02)	0.009
Global cognition	0.04	(0.03)	0.08	(0.04)	-0.03	(0.03)	0.04	(0.03)	0.03	(0.02)	0.003
Beer											
Word recall	-0.01	(0.05)	0.13*	(0.07)	-0.16**	(0.05)	-0.07	(0.06)	-0.03	(0.03)	0.017
Verbal fluency	-0.10*	(0.05)	-0.03	(0.07)	-0.17**	(0.06)	-0.06	(0.06)	-0.09**	(0.03)	
Letter search	0.01	(0.05)	-0.00	(0.08)	-0.09	(0.06)	0.02	(0.06)	-0.00	(0.03)	
Delayed recall	0.05	(0.05)	0.12	(0.07)	-0.16**	(0.06)	-0.02	(0.06)	-0.01	(0.03)	0.004
Global cognition	-0.01	(0.03)	0.06	(0.05)	-0.14***	(0.04)	-0.03	(0.04)	-0.03	(0.02)	0.007
Spirits											
Word recall	-0.20*	(0.08)	-0.12	(0.06)	-0.15*	(0.06)	0.09*	(0.03)	-0.01	(0.03)	<0.001
Verbal fluency	0.05	(0.09)	-0.12	(0.07)	-0.11	(0.06)	0.05	(0.04)	-0.00	(0.03)	0.026
Letter search	-0.10	(0.09)	-0.06	(0.07)	-0.03	(0.07)	0.03	(0.04)	0.00	(0.03)	
Delayed recall	-0.28**	(0.09)	-0.06	(0.06)	-0.12	(0.06)	0.05	(0.04)	-0.01	(0.03)	<0.001
Global cognition	-0.13*	(0.06)	-0.09*	(0.05)	-0.10*	(0.04)	0.05*	(0.02)	-0.01	(0.02)	<0.001
N	**2379**		**3205**		**2465**		**3489**		**11544**		

b=regression coefficient; SE=standard error.
Reference group is drinkers of other types of alcohol.
All models are adjusted for total alcohol intake, age, education, assets, smoking, measurement wave, and, if pooled, centre.
P-value is for interaction alcohol type*centre (only p-values <0.05 are shown).
* p <0.05, ** p <0.01, *** p <0.001

Results for alcohol type and cognitive function are shown in Table 4.14. These analyses were restricted to drinkers only. After multivariable adjustment (alcohol volume, age, education, household assets and smoking), alcohol type was not consistently associated with cognitive performance. In pooled analysis only beer drinking vs. not drinking beer in women was significantly associated with lower verbal fluency scores ($p<0.01$). In men, there was an indication of better verbal fluency and global cognitive scores in wine drinkers and lower word recall scores in spirit drinkers but these associations were rather weak and statistically significant at 5% level only in the pooled sample with high statistical power. There was significant heterogeneity among study centres for some combinations of alcohol type and cognitive function as indicated by p-values for interactions between alcohol type and study centre, particularly in women (far-right column in Table 4.14.).

In additional analyses further adjustments for cardiovascular risk factors (BMI, systolic and diastolic blood pressure, resting pulse and high and low-density lipoproteins) from the baseline clinical examination did not materially change the associations between alcohol indices and cognitive outcomes. The number of participants included in these analyses was 24,263 after listwise deletion on all variables in the model, resulting from significant numbers of missing values in the clinical examination measures (not all participants who completed the questionnaire, attended the examination) (see Appendix VI).

Additional Tobit regression analyses of alcohol indices and delayed recall gave very similar results, suggesting that possible ceiling effects (15.4% of participants scored at ceiling in the sample as a whole) did not bias multiple linear regression estimates for this cognitive measure.

Additional analyses in Krakow, Kaunas and Novosibirsk adjusting for the presence of hearing, vision or other problems that might have interfered with cognitive testing did not significantly affect the results on alcohol and cognitive function; these data were not collected in the Czech sample, and were thus not included in the main analysis.

4.3.3. Past drinking behaviour and cognitive function in Novosibirsk

Analyses in the previous section have shown a near-linear positive association between drinking frequency and verbal cognitive measures in women and a modest positive association in males at moderate intakes or occasional heavy drinking pattern. In addition, a statistically significant negative association with high alcohol intake was observed for some cognitive measures in men, and significantly worse cognitive scores were also observed in Czech and Polish non-drinkers. It has been suggested that the association between alcohol consumption and cognitive function may be biased by past drinking behaviour, particularly the resulting misclassification of former drinkers with poor health among non-drinkers. Results from analyses of past drinking behaviour and cognitive function in Novosibirsk, where relevant data on past drinking were collected at both baseline and follow-up, are presented in this section.

4.3.3.1. Descriptive results

As seen in Table 4.15., descriptive results for past drinking behaviour in Novosibirsk suggest that very few men (just under 1 %) in the sample were stable non-drinkers, compared to

almost 8% of women. Since there were so few heavy drinkers (average intake of >20 g per day) among women, it was not feasible to distinguish between stable and reduced use drinkers in the high alcohol consumption group in women. Nearly a half of former drinkers reported giving up drinking because of reasons related to poor health. Among current drinkers, 52.2% of men and 39.2% of women reported drinking more in the past.

Table 4.15. Descriptive results for past alcohol use and cognitive function in Novosibirsk

	Novosibirsk					
	Men		Women		Total	
	N	%	N	%	N	%
Change in alcohol use						
Stable non-drinker	26	0.9	302	7.7	328	4.7
Former drinker - health	144	5.2	169	4.3	313	4.5
Former drinker - other	181	6.5	171	4.4	352	5.1
Stable drinker	1157	41.8	1745	44.8	2902	41.7
Reduced use drinker	1262	45.6	1124	28.8	2386	34.3
Observations (data present)	3063	90.4	3899	90.1	6281	90.2
Past use vs. current alcohol intake						
Stable non-drinker	26	0.9	302	8.6	328	5.2
Former drinker - health	144	5.2	169	4.8	313	5.0
Former drinker - other	181	6.5	171	4.9	352	5.6
Stable light	605	21.8	1544	44.0	2149	34.2
Stable moderate	425	15.3	201	5.7	626	10.0
Stable heavy	127	4.6	na	na	127	2.0
Reduced use light	830	30.0	1051	29.9	1881	29.9
Reduced use moderate	350	12.6	73	2.1	423	6.7
Reduced use heavy	82	3.0	na	na	82	1.3
Past use vs. current drinking frequency						
Stable non-drinker	26	0.9	302	8.6	328	5.2
Former drinker - health	144	5.2	169	4.8	313	5.0
Former drinker - other	181	6.5	171	4.9	352	5.6
Stable <1 per week	480	17.3	1584	45.1	2064	32.9
Stable ≥1 per week	677	24.4	161	4.6	838	13.3
Reduced use <1 per week	700	25.3	1058	30.1	1758	28.0
Reduced use ≥1 per week	562	20.3	66	1.9	628	10.0

Figures are counts and proportions.

Corresponding proportions reporting drinking more in the past were in 57.8%, 45.2% and 39.2% in light, moderate and heavy male drinkers, respectively. In women, 40.5% of current light drinkers and 26.6% of current moderate-to-heavy drinkers reported higher past alcohol consumption.

4.3.3.2. Regression analysis

Regression analyses of past drinking behaviour and past drinking behaviour cross-classified by current alcohol consumption are shown in Table 4.16. for men and women. The models were adjusted for main potential confounders (age, education, household assets and smoking). In both men and women, former drinkers who quit because of health-related reasons had significantly lower cognitive scores on word recall, delayed recall and global cognition and non-significantly lower scores on letter search and verbal fluency, compared to stable (light or infrequent) drinkers. Former drinkers who quit because of other reasons were not significantly different from stable (light or infrequent) drinkers and, in men, actually showed non-significantly better performance on most tests of cognition. In women, stable non-drinkers also had significantly lower cognitive scores on several tests. In men, cognitive scores were not significantly different in stable non-drinkers but only very few participants were in this category (≈1 %).

As expected, in additional models further adjusted for health status measures (self-rated health, history or presence of chronic conditions (CVD, stroke, diabetes, and hypertension)) the association with cognitive function in former drinkers who quit because of health-related reasons was markedly attenuated (see Appendix IX). In women, the association in stable non-drinkers was also attenuated after adjustment for health factors but to a lesser degree. Adjustment for basic health status measures markedly attenuated but did not always eliminate the negative association in former drinkers who quit drinking because of health-related reasons.

Table 4.16. Regression estimates for associations of past alcohol use and cognitive function in Novosibirsk

	Word recall		Verbal fluency		Letter search		Delayed recall		Global cognition	
	b	SE	b	SE	b	SE	b	SE	b	SE
Men (n=2,770)										
Past alcohol use										
Stable non-drinker	-0.10	(0.17)	-0.01	(0.17)	-0.08	(0.18)	0.01	(0.17)	-0.04	(0.12)
Former drinker - health	-0.32***	(0.08)	-0.13	(0.08)	-0.06	(0.08)	-0.28***	(0.07)	-0.20***	(0.05)
Former drinker - other	0.04	(0.07)	0.09	(0.07)	0.01	(0.07)	0.06	(0.07)	0.05	(0.05)
Stable drinker	0.00		0.00		0.00		0.00		0.00	
Reduced use drinker	-0.04	(0.03)	0.03	(0.04)	-0.06	(0.04)	0.02	(0.03)	-0.01	(0.02)
Past use vs. frequency										
Stable non-drinker	-0.04	(0.17)	0.02	(0.18)	-0.12	(0.18)	0.07	(0.17)	-0.02	(0.12)
Former drinker - Health	-0.26**	(0.08)	-0.09	(0.08)	-0.10	(0.09)	-0.23**	(0.08)	-0.17**	(0.06)
Former drinker - Other	0.10	(0.07)	0.13	(0.08)	-0.03	(0.08)	0.11	(0.07)	0.08	(0.05)
Stable <1 pw	0.00		0.00		0.00		0.00		0.00	
Stable ≥1 pw	0.10*	(0.05)	0.07	(0.05)	-0.07	(0.05)	0.09	(0.05)	0.05	(0.04)
Reduced use <1 pw	0.04	(0.05)	0.04	(0.05)	-0.09	(0.05)	0.10*	(0.05)	0.02	(0.04)
Reduced use ≥1 pw	0.01	(0.05)	0.10	(0.06)	-0.12*	(0.06)	0.05	(0.05)	0.01	(0.04)
Past use vs. intake										
Stable non-drinker	-0.07	(0.17)	-0.00	(0.18)	-0.10	(0.18)	0.03	(0.17)	-0.03	(0.12)
Former drinker - Health	-0.29***	(0.08)	-0.12	(0.08)	-0.08	(0.08)	-0.26***	(0.08)	-0.19**	(0.06)
Former drinker - Other	0.07	(0.07)	0.11	(0.08)	-0.01	(0.08)	0.08	(0.07)	0.06	(0.05)
Stable <10 g /day	0.00		0.00		0.00		0.00		0.00	
Stable 10-40 g /day	0.05	(0.05)	0.05	(0.06)	0.00	(0.06)	0.05	(0.05)	0.04	(0.04)
Stable >40 g /day	0.09	(0.08)	-0.01	(0.09)	-0.23**	(0.09)	-0.01	(0.08)	-0.04	(0.06)
Reduced use <10 g /day	-0.00	(0.05)	0.00	(0.05)	-0.10*	(0.05)	0.06	(0.05)	-0.01	(0.03)
Reduced use 10-40 g /day	-0.01	(0.06)	0.15*	(0.06)	-0.07	(0.06)	-0.00	(0.06)	0.02	(0.04)
Reduced use >40 g /day	-0.08	(0.10)	-0.00	(0.11)	-0.07	(0.11)	0.03	(0.10)	-0.03	(0.07)
Women (n=3,511)										
Past alcohol use										
Stable non-drinker	-0.14**	(0.05)	-0.15**	(0.05)	-0.05	(0.06)	-0.12*	(0.05)	-0.12**	(0.04)
Former drinker - health	-0.20**	(0.07)	-0.09	(0.07)	-0.09	(0.08)	-0.20**	(0.07)	-0.14**	(0.05)
Former drinker - other	-0.01	(0.07)	0.03	(0.07)	-0.10	(0.07)	-0.06	(0.07)	-0.03	(0.05)
Stable drinker	0.00		0.00		0.00		0.00		0.00	
Reduced use drinker	-0.01	(0.03)	0.06	(0.03)	0.02	(0.04)	0.01	(0.03)	0.02	(0.02)
Past use vs. frequency										
Stable non-drinker	-0.14**	(0.05)	-0.15**	(0.05)	-0.04	(0.06)	-0.12*	(0.05)	-0.11**	(0.04)
Former drinker - Health	-0.20**	(0.07)	-0.08	(0.07)	-0.08	(0.08)	-0.20**	(0.07)	-0.14**	(0.05)
Former drinker - Other	-0.01	(0.07)	0.04	(0.07)	-0.10	(0.08)	-0.05	(0.07)	-0.03	(0.05)
Stable <1 pw	0.00		0.00		0.00		0.00		0.00	
Stable ≥1 pw	-0.03	(0.07)	0.04	(0.07)	0.07	(0.08)	0.08	(0.07)	0.04	(0.05)
Reduced use <1 pw	-0.02	(0.03)	0.07*	(0.03)	0.03	(0.04)	0.01	(0.03)	0.02	(0.02)
Reduced use ≥1 pw	0.17	(0.11)	-0.13	(0.11)	0.11	(0.12)	0.08	(0.11)	0.06	(0.08)
Past use vs. intake										
Stable non-drinker	-0.14**	(0.05)	-0.15**	(0.05)	-0.04	(0.06)	-0.11*	(0.05)	-0.11**	(0.04)
Former drinker - Health	-0.20**	(0.07)	-0.09	(0.07)	-0.08	(0.08)	-0.19**	(0.07)	-0.14**	(0.05)
Former drinker - Other	-0.01	(0.07)	0.03	(0.07)	-0.10	(0.08)	-0.05	(0.07)	-0.03	(0.05)
Stable <5 g /day	0.00		0.00		0.00		0.00		0.00	
Stable >5 g /day	0.00	(0.06)	0.02	(0.07)	0.03	(0.07)	0.10	(0.06)	0.04	(0.05)
Reduced use <5 g /day	-0.02	(0.03)	0.07*	(0.03)	0.03	(0.04)	0.01	(0.03)	0.02	(0.02)
Reduced use >5 g /day	0.17	(0.10)	-0.13	(0.11)	0.07	(0.11)	0.13	(0.10)	0.06	(0.07)

b=regression coefficient; SE=standard error.
Reference group is stable light or infrequent drinker.
All models are adjusted for age, education, assets, smoking and measurement wave.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Among drinkers, cognitive performance in reduced use drinkers did not appear to be consistently worse (or better) compared to stable drinkers in both genders. With the exception of letter search in men, in these analyses the association with cognitive scores in drinkers was generally positive at higher intakes and drinking frequencies but not highest intakes (in men). However, this association was not always consistent and was mostly non-significant.

Sensitivity analyses of past drinking behaviour restricted to participants, whose cognitive measurement was completed at baseline, gave very similar results and are presented in Appendix X, on pg. 264.

Table 4.17. shows results for total alcohol intake in relation to cognitive test scores in Novosibirsk before and after excluding reduced use drinkers and former drinkers who quit for health reasons. The models are adjusted for main potential confounders (age, education, assets and smoking). Echoing the results of pooled regression analyses presented in the preceding section, a non-significant inverse U-shaped relationship was generally observed between cognitive performance and alcohol intake in Novosibirsk. However, it should be noted that the results for female heavy drinkers may be less reliable, since there were very few in the sample. In Novosibirsk, female non-drinkers showed significantly worse cognitive performance than light drinkers. With the exception of word recall ($p<0.05$), male non-drinkers had non-significantly worse cognitive scores, compared to light drinkers. In contrast, in analyses excluding former drinkers who quit drinking because of poor health, male non-drinkers showed non-significantly better cognitive performance, compared to light or infrequent drinkers. In women, non-drinkers still showed significantly worse cognitive performance than light or infrequent drinkers but the difference was attenuated after excluding former drinkers who quit drinking because of poor health.

Table 4.17. Regression estimates from analyses of alcohol and cognitive function in Novosibirsk, before and after exclusions

	Word recall		Verbal fluency		Letter search		Delayed recall		Global cognition	
	b	SE	b	SE	b	SE	b	SE	b	SE
Men										
No exclusions (n=3,063)										
Alcohol intake										
Non-drinker	-0.10*	(0.05)	-0.01	(0.05)	-0.03	(0.05)	-0.09	(0.05)	-0.06	(0.03)
<10 g /day	0.00		0.00		0.00		0.00		0.00	
10-40 g /day	0.02	(0.04)	0.08	(0.04)	0.00	(0.04)	-0.01	(0.04)	0.02	(0.03)
>40 g /day	0.02	(0.06)	-0.02	(0.06)	-0.14*	(0.06)	-0.05	(0.06)	-0.04	(0.04)
Excluding former drinkers with poor health (n=2,657)										
Alcohol intake										
Non-drinker	0.00	(0.06)	0.08	(0.06)	0.01	(0.06)	0.02	(0.06)	0.03	(0.04)
<10 g /day	0.00		0.00		0.00		0.00		0.00	
10-40 g /day	0.01	(0.04)	0.09*	(0.04)	-0.00	(0.04)	-0.00	(0.04)	0.02	(0.03)
>40 g /day	0.00	(0.06)	-0.03	(0.06)	-0.15*	(0.06)	-0.04	(0.06)	-0.05	(0.04)
Excluding reduced use drinkers (n=1,801)										
Alcohol intake										
Non-drinker	-0.11*	(0.05)	-0.02	(0.06)	-0.10	(0.06)	-0.08	(0.05)	-0.08*	(0.04)
<10 g /day	0.00		0.00		0.00		0.00		0.00	
10-40 g /day	0.04	(0.05)	0.03	(0.05)	-0.03	(0.05)	0.04	(0.05)	0.02	(0.04)
>40 g /day	0.07	(0.08)	-0.02	(0.08)	-0.26**	(0.08)	-0.04	(0.07)	-0.06	(0.05)
Women										
No exclusions (n=3,463)										
Alcohol intake										
Non-drinker	-0.12***	(0.04)	-0.12**	(0.04)	-0.08	(0.04)	-0.13***	(0.04)	-0.11***	(0.03)
<5 g /day	0.00		0.00		0.00		0.00		0.00	
5-20 g /day	0.07	(0.05)	-0.06	(0.06)	0.01	(0.06)	0.10	(0.05)	0.03	(0.04)
>20 g /day	-0.17	(0.13)	0.05	(0.14)	-0.07	(0.15)	-0.05	(0.13)	-0.06	(0.10)
Excluding former drinkers with poor health (n=3,463)										
Alcohol intake										
Non-drinker	-0.09*	(0.04)	-0.10*	(0.04)	-0.07	(0.05)	-0.10*	(0.04)	-0.09**	(0.03)
<5 g /day	0.00		0.00		0.00		0.00		0.00	
5-20 g /day	0.07	(0.05)	-0.06	(0.06)	0.00	(0.06)	0.09	(0.05)	0.03	(0.04)
>20 g /day	-0.18	(0.14)	-0.03	(0.15)	-0.07	(0.15)	-0.04	(0.14)	-0.08	(0.10)
Excluding reduced use drinkers (n=2,775)										
Alcohol intake										
Non-drinker	-0.13***	(0.04)	-0.12**	(0.04)	-0.07	(0.04)	-0.13***	(0.04)	-0.11***	(0.03)
<5 g /day	0.00		0.00		0.00		0.00		0.00	
5-20 g /day	0.03	(0.06)	-0.01	(0.06)	0.02	(0.07)	0.09	(0.06)	0.03	(0.04)
>20 g /day	-0.22	(0.16)	0.20	(0.16)	-0.26	(0.17)	-0.06	(0.15)	-0.08	(0.11)

b=regression coefficient; SE=standard error.
The models are adjusted for age, education, assets, smoking and measurement wave.
Reference group is light drinker (<5/10 g daily).
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

In addition, analyses restricted to stable drinkers produced a similar overall pattern of results. Heavy drinkers generally still had lower cognitive scores compared to light drinkers, while the cognitive score difference between light and moderate drinkers was attenuated for some but not all cognitive measures.

4.4. Smoking and cognitive function

Finally, in this section the results of analysis on smoking behaviour and mid to late life cognitive function are presented.

4.4.1. Descriptive results

The number of participants with complete data was 26,921 for analyses of smoking status and 26,241 for analyses of pack years, and cognitive function. The sample size for analyses of pack years is smaller because not all participants, who reported smoking status, also had complete data on all variables required for calculating pack years. Participants with missing data for cognitive function were more likely to smoke ($p<0.001$) and had higher number of pack years of smoking ($p<0.001$) compared to participants, who had cognitive function data.

Table 4.18. Sample distributions of smoking variables (n=26,921)

	Men (n=12,388)					Women (n=14,533)				
	Czech towns	Novosibirsk	Krakow	Kaunas	Total	Czech towns	Novosibirsk	Krakow	Kaunas	Total
Smoking status, (%)										
Never smoked	33.3	25.9	27.2	38.5	30.9	56.2	86.9	51.8	82.9	70.2
Current smoker	25.2	46.3	31.6	30.2	33.5	20.5	8.3	24.1	9.9	15.4
Former smoker	41.5	27.9	41.2	31.2	35.5	23.3	4.9	24.1	7.3	14.4
Pack years	16.5 (19.3)	24.2 (22.6)	24.8 (24.5)	16.1 (19.5)	20.8 (22.2)	6.9 (11.9)	1.4 (5.2)	10.7 (16.0)	1.8 (6.3)	5.1 (11.4)

Figures are proportions or means with standard deviations in parentheses.

Prevalence of current and ever smoking was high among men; 33% were current smokers and 36% were former smokers. The highest prevalence of current smoking was found in Novosibirsk men and the lowest in Czech men. Women in these cohorts were significantly less likely to smoke or to be former smokers. Among women 16% were current smokers, ranging from 9% in Novosibirsk to 25% in Krakow. Significant gender differences (chi square $p<0.001$) in smoking rates were found in all centres but were most pronounced in Novosibirsk and Kaunas.

In men, the average age at starting smoking was 19.1 years and 18.7 years in current and former smokers (current vs. former two-tailed t-test $p=0.002$), compared to 23.3 and 22.1 years in women ($p<0.001$). Average age at quitting smoking in former smokers was 44.1 years in men and 44.4 years in women, respectively. The average number of cigarettes smoked daily by current smokers was 17.0 in men and 11.9 in women. Corresponding numbers for former smokers were 20.3 and 12.4 cigarettes per day. Thus, all smoking behaviours were more favourable in women than in men, with the exception of age at quitting smoking in former smokers for which there was no difference (t-test $p=0.437$).

Table 4.19. shows characteristics of the study population for men and women in the sample as a whole stratified by smoking status. In men, smoking was significantly associated with verbal fluency and letter search, borderline associated with immediate ($p=0.038$) and delayed ($p=0.040$) recall, and not associated with global cognition. In men, smoking was also associated with age, education, assets, alcohol use, self-rated health and self-reported medical conditions. In women, significant unadjusted associations were observed between smoking status and all cognitive outcomes but not in the expected direction. Smoking status was also associated with age, education, assets, alcohol use and all health measures.

Table 4.19. Characteristics of study population grouped by smoking status

	Total		Smoking status						
			Never smoked		Current smoker		Former smoker		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p-value
Men									
Age at starting smoking	NA	NA	NA	NA	19.0	(6.0)	18.7	(4.7)	0.002
Age at quitting smoking	NA	NA	NA	NA	NA	NA	44.1	(12.3)	NA
Number of cigarettes smoked	NA	NA	NA	NA	17.0	(8.8)	20.3	(12.4)	<0.001
Pack years of smoking	20.8	(22.2)	0.0	(0.0)	34.1	(18.8)	27.0	(21.8)	<0.001
Word recall	20.6	(4.3)	20.8	(4.2)	20.6	(4.4)	20.6	(4.2)	<0.001
Verbal fluency	21.3	(6.8)	21.4	(6.8)	20.9	(6.9)	21.4	(6.7)	<0.001
Letter search	16.7	(5.2)	16.9	(5.0)	16.4	(5.3)	16.8	(5.1)	<0.001
Delayed recall	7.0	(2.0)	7.1	(1.9)	7.0	(2.0)	7.0	(1.9)	0.040
Global cognition	0.02	(0.8)	0.04	(0.8)	0.01	(0.8)	0.01	(0.8)	0.091
Age	60.3	(6.5)	61.1	(6.5)	58.7	(6.4)	61.2	(6.3)	<0.001
Education, (%)									<0.001
Primary or less	9.7		8.2		11.2		9.5		
Secondary	59.9		51.0		65.8		62.1		
University	30.4		40.8		23.1		28.4		
Household assets	6.5	(2.1)	6.7	(2.1)	6.2	(2.1)	6.7	(2.0)	<0.001
Alcohol intake, (%)									<0.001
Non-drinker	11.3		10.7		10.6		12.4		
Light drinker	54.0		61.4		47.7		53.5		
Moderate drinker	28.8		25.1		32.7		28.2		
Heavy drinker	6.0		2.8		9.1		5.8		
Self-rated health	3.2	(0.7)	3.3	(0.7)	3.2	(0.7)	3.2	(0.7)	<0.001
Medical history									
MI, (%)	10.3		7.7		9.1		13.8		<0.001
Angina/ISH, (%)	14.0		11.0		12.1		18.3		<0.001
Stroke, (%)	3.7		3.1		3.4		4.6		0.001
High blood pressure, (%)	55.1		55.9		47.0		62.1		<0.001
Diabetes, (%)	9.9		8.3		6.9		14.0		<0.001
N	**12,435**		**3,990**		**4,154**		**4,290**		
Women									
Age at starting smoking	NA	NA	NA	NA	23.2	(7.6)	22.1	(6.2)	<0.001
Age at quitting smoking	NA	NA	NA	NA	NA	NA	44.4	(11.9)	NA
Number of cigarettes smoked	NA	NA	NA	NA	11.9	(7.0)	12.4	(9.4)	0.049
Pack years of smoking	5.1	(11.4)	0.0	(0.0)	20.8	(14.3)	14.7	(15.1)	<0.001
Word recall	22.1	(4.1)	21.8	(4.1)	22.6	(4.0)	22.7	(3.9)	<0.001
Verbal fluency	21.0	(6.6)	20.4	(6.6)	22.3	(6.5)	22.8	(6.4)	<0.001
Letter search	17.9	(5.3)	17.6	(5.3)	18.4	(5.1)	18.8	(5.4)	<0.001
Delayed recall	7.6	(1.9)	7.5	(1.9)	7.8	(1.8)	7.9	(1.8)	<0.001
Global cognition	0.01	(0.8)	-0.04	(0.8)	0.12	(0.7)	0.15	(0.7)	<0.001
Age	59.9	(6.6)	60.8	(6.5)	56.7	(5.9)	58.8	(6.1)	<0.001
Education, (%)									<0.001
Primary	12.5		13.3		10.1		11.4		
Secondary	62.2		61.1		66.5		63.2		
University	25.2		25.6		23.5		25.4		
Household assets	6.0	(2.1)	5.8	(2.1)	6.3	(2.0)	6.4	(2.0)	<0.001
Alcohol intake, (%)									<0.001
Non-drinker	20.2		20.5		18.9		20.2		
Light drinker	63.3		66.6		55.9		55.6		
Moderate drinker	13.5		10.9		19.9		19.3		
Heavy drinker	3.0		2.0		5.4		4.9		
Self-rated health	3.1	(0.7)	3.0	(0.7)	3.3	(0.8)	3.2	(0.8)	<0.001
Medical history									
MI, (%)	4.5		4.7		3.3		4.9		0.006
Angina/ISH, (%)	14.3		15.6		9.8		13.2		<0.001
Stroke, (%)	3.2		3.5		1.7		3.3		<0.001
High blood pressure, (%)	59.1		62.7		45.4		56.3		<0.001
Diabetes, (%)	8.9		9.1		6.2		10.7		<0.001
N	**14,591**		**10,398**		**2,244**		**1,949**		

NA=not applicable

Figures are means with standard deviations in parentheses or proportions, as appropriate.

P-values are from t-test, ANOVA and chi-square test, as appropriate.

In both genders current smokers were younger than never smokers (2.4 years in men and 4.1 years in women), and female former smokers were also younger than never smokers. Although differences in education and material circumstances across smoking status were statistically significant in both genders, the degree of social patterning appeared to be much greater in men. Among men 40.8% of never smokers had university education, compared to only 23.1% of current smokers, while in women the difference in proportion with university education between never and current smokers was only 2%. In men, unadjusted mean number of household assets owned was lower in current smokers than in never or former smokers, while in women the association was in the opposite direction.

4.4.2. Regression analysis

Results from pooled regression analyses of smoking status and cognitive function are shown in Table 4.20. and Table 4.21. for men and women, respectively. In age-adjusted models male current smokers had lower scores on all cognitive tests and worse global cognition (all $p<0.001$). After adjustment for socioeconomic confounders, education and household assets, these associations were no longer significant for three out of four cognitive tests and global cognition. Current smoking remained significantly associated with poorer search speed performance ($p<0.001$), although the association was notably attenuated after adjusting for SEP measures. This association was attenuated somewhat further by additional adjustments for alcohol intake and heath measures but remained statistically significant ($p<0.01$). In age-adjusted models male former smokers had significantly lower cognitive scores on tests of immediate recall, mental speed and global cognition (all $p<0.05$). After adjusting for

Table 4.20. Pooled regression estimates for cognitive function and smoking in men (n=12,388)

	Model 1: Age		Model 2: Education, assets		Model 3: Alcohol		Model 4: Health		
	b	SE	b	SE	b	SE	b	SE	p-value
Word recall									
Smoking status									0.759
Never smoker	0.00		0.00		0.00		0.00		
Current smoker	-0.15***	(0.02)	-0.02	(0.02)	-0.03	(0.02)	-0.02	(0.02)	
Former smoker	-0.04*	(0.02)	0.01	(0.02)	0.01	(0.02)	0.04	(0.02)	
Verbal fluency									
Smoking status									0.195
Never smoker	0.00		0.00		0.00		0.00		
Current smoker	-0.12***	(0.02)	0.00	(0.02)	-0.00	(0.02)	0.01	(0.02)	
Former smoker	-0.01	(0.02)	0.04*	(0.02)	0.04*	(0.02)	0.06**	(0.02)	
Letter search									
Smoking status									0.026
Never smoker	0.00		0.00		0.00		0.00		
Current smoker	-0.20***	(0.02)	-0.07***	(0.02)	-0.07***	(0.02)	-0.06**	(0.02)	
Former smoker	-0.06**	(0.02)	-0.00	(0.02)	0.00	(0.02)	0.02	(0.02)	
Delayed recall									
Smoking status									0.170
Never smoker	0.00		0.00		0.00		0.00		
Current smoker	-0.09***	(0.02)	0.01	(0.02)	0.01	(0.02)	0.02	(0.02)	
Former smoker	-0.04	(0.02)	0.00	(0.02)	0.00	(0.02)	0.02	(0.02)	
Global cognition									
Smoking status									0.089
Never smoker	0.00		0.00		0.00		0.00		
Current smoker	-0.14***	(0.02)	-0.02	(0.02)	-0.03	(0.02)	-0.01	(0.02)	
Former smoker	-0.04*	(0.02)	0.01	(0.01)	0.02	(0.01)	0.03*	(0.01)	

b=regression coefficient; SE=standard error.
Reference group is never smoker.
Model 1: Age-adjusted.
Model 2: Additionally adjusted for education and assets.
Model 3: Additionally adjusted for alcohol volume.
Model 4: Additionally adjusted for self-rated health and self-reported medical history.
All models also adjusted for centre and measurement wave.
Far-right column: p-value is for interaction smoking*centre for the fully adjusted model.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

socioeconomic covariates, regression coefficients for former smokers actually turned positive for several cognitive tests, compared to never smokers.

The presence of a borderline significant interaction (p=0.026, fully adjusted model) between smoking status and centre for letter search indicates a degree of heterogeneity between study centres in the effect of smoking on letter search speed in men. In analyses stratified by centre, current smoking was not associated with letter search in Krakow, Czech smokers showed non-significantly lower scores, and smokers in Novosibirsk and Kaunas had significantly reduced scores of similar magnitude (shown in Appendix XII, pg. 267).

Table 4.21. Pooled regression estimates for cognitive function and smoking in women (n=14,533)

	Model 1: Age		Model 2: Education, assets		Model 3: Alcohol		Model 4: Health		
	b	SE	b	SE	b	SE	b	SE	p-value
Word recall									
Smoking status									0.301
Never smoker	0.00		0.00		0.00		0.00		
Current smoker	-0.02	(0.02)	-0.01	(0.02)	-0.02	(0.02)	-0.02	(0.02)	
Former smoker	0.08***	(0.02)	0.07**	(0.02)	0.05**	(0.02)	0.06**	(0.02)	
Verbal fluency									
Smoking status									0.006
Never smoker	0.00		0.00		0.00		0.00		
Current smoker	-0.01	(0.02)	0.01	(0.02)	0.00	(0.02)	0.00	(0.02)	
Former smoker	0.14***	(0.02)	0.12***	(0.02)	0.11***	(0.02)	0.11***	(0.02)	
Letter search									
Smoking status									
Never smoker	0.00		0.00		0.00		0.00		0.060
Current smoker	-0.07**	(0.02)	-0.06**	(0.02)	-0.06**	(0.02)	-0.07**	(0.02)	
Former smoker	0.07**	(0.02)	0.06*	(0.02)	0.05*	(0.02)	0.06*	(0.02)	
Delayed recall									
Smoking status									
Never smoker	0.00		0.00		0.00		0.00		0.002
Current smoker	-0.03	(0.02)	-0.01	(0.02)	-0.02	(0.02)	-0.02	(0.02)	
Former smoker	0.08***	(0.02)	0.07**	(0.02)	0.06**	(0.02)	0.07**	(0.02)	
Global cognition									
Smoking status									
Never smoker	0.00		0.00		0.00		0.00		0.269
Current smoker	-0.03	(0.02)	-0.01	(0.02)	-0.02	(0.02)	-0.02	(0.02)	
Former smoker	0.09***	(0.02)	0.08***	(0.02)	0.07***	(0.02)	0.08***	(0.02)	

b=regression coefficient; SE=standard error.
Reference group is never smoker.
Model 1: Age-adjusted.
Model 2: Additionally adjusted for education and assets.
Model 3: Additionally adjusted for alcohol volume.
Model 4: Additionally adjusted for self-rated health and self-reported medical history.
All models also adjusted for centre and measurement wave.
Far-right column: p-value is for interaction smoking*centre for the fully adjusted model.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

In women, only letter search showed a significant negative association with current smoking in age-adjusted models ($p<0.01$), and this association remained significant after adjusting for covariates ($p<0.01$). For other cognitive measures the non-significant associations in current smokers were generally in the expected direction but very weak. Female former smokers had significantly better cognitive scores on all tests, compared to never smokers. These associations were modestly attenuated after adjustments for socioeconomic factors and alcohol intake, and slightly strengthened after adjusting for health-related factors.

In women, there was significant heterogeneity between centres for verbal fluency and delayed recall; in stratified models current smokers in Novosibirsk had comparably higher verbal fluency scores and current smokers in Krakow had significantly lower delayed recall scores than never smokers but this was not observed in other centres.

In men, there was no indication that associations between smoking status and cognitive function varied by age, whereas in women significant interactions were observed. Post hoc analyses stratified by 10-year age groups generally showed higher cognitive scores in older middle-aged (aged 55-64) current and former smokers, compared to their younger middle-aged (age 45-54) and older (65+) counterparts for letter search, immediate recall and delayed recall. In fact, for letter search cognitive scores in current older middle-aged female smokers were not significantly different from scores in never smokers.

Table 4.22. shows associations between pack years of smoking and cognitive measures. In age-adjusted models lower cognitive scores were observed with increasing pack years in men for all measures, suggesting a dose-response relationship. After adjusting for socioeconomic factors, significant but notably weakened association remained only between pack years of smoking and letter search speed. This association was further attenuated and became statistically insignificant after additional adjustment for health measures. There was no consistent relationship between pack years of smoking and cognitive performance in women. Pack years of smoking generally showed a positive relationship with cognitive scores in women, particularly after adjusting for socioeconomic and other covariates.

In men, there was significant heterogeneity among centres for letter search, with increasing pack years having a greater effect in Novosibirsk and Kaunas; in these two centres

associations remained statistically significant after adjusting for confounders and health measures (shown in Appendix XII, pg. 267).

Table 4.22. Pooled regression estimates for pack years of smoking and cognitive function

	Model 1: Age		Model 2: Education, assets		Model 3: Alcohol		Model 4: Health		
	b	SE	b	SE	b	SE	b	SE	p-value
Men (n=12,029)									
Word recall	-0.002***	(0.00)	-0.000	(0.00)	-0.000	(0.00)	0.000	(0.00)	
Verbal fluency	-0.001*	(0.00)	0.001*	(0.00)	0.001*	(0.00)	0.001**	(0.00)	
Letter search	-0.003***	(0.00)	-0.001*	(0.00)	-0.001*	(0.00)	-0.000	(0.00)	0.003
Delayed recall	-0.001**	(0.00)	0.000	(0.00)	0.000	(0.00)	0.001	(0.00)	
Global cognition	-0.002***	(0.00)	-0.000	(0.00)	-0.000	(0.00)	0.000	(0.00)	
Women (n=14,274)									
Word recall	0.000	(0.00)	0.001	(0.00)	0.001	(0.00)	0.001	(0.00)	
Verbal fluency	0.001	(0.00)	0.002**	(0.00)	0.002*	(0.00)	0.002**	(0.00)	
Letter search	-0.000	(0.00)	0.000	(0.00)	0.000	(0.00)	0.000	(0.00)	
Delayed recall	-0.000	(0.00)	0.000	(0.00)	0.000	(0.00)	0.000	(0.00)	
Global cognition	0.000	(0.00)	0.001	(0.00)	0.001	(0.00)	0.001	(0.00)	

b=regression coefficient; SE=standard error.
Model 1: Age-adjusted.
Model 2: Additionally adjusted for education and assets.
Model 3: Additionally adjusted for alcohol volume.
Model 4: Additionally adjusted for self-rated health and self-reported medical history.
All models also adjusted for centre and measurement wave.
Far-right column: p-value is for interaction smoking*centre for the fully adjusted model.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Additional analyses with pack years categorized into centre-specific quintiles, allowing for non-linearity, gave very similar results (as seen in Appendix XI, pg. 265). Associations between pack years of smoking and cognitive function showed a similar pattern but were even weaker in further analyses restricted to current smokers or ever smokers. When the analyses were restricted to current or ever smokers, there were no significant interactions by study centre in the association between pack years of smoking and cognitive tests, suggesting that heterogeneity was driven by the inclusion of long-term non-smokers. There was very little evidence overall of a dose-response relationship between pack years of smoking and cognitive function.

Further adjustments for two other potential confounders, leisure-time physical activity and high depressive symptoms did not significantly change the results for smoking status and cognitive function. Additionally, analyses with further adjustments for cardiovascular risk factors (BMI, systolic and diastolic blood pressure, resting pulse, and high and low-density lipoproteins) from the baseline clinical examination did not explain the associations between smoking status and reduced scores on the visual search task. Numbers of participants with complete data included in these two sets of analyses were 26,022 and 24,155 for additional confounders and vascular factors, respectively.

Results of exploratory analyses with alternative ways of measuring smoking (e.g. daily number of cigarettes smoked; distinguishing between long-term ex-smokers and recent quitters) were similar to the results presented here and did not convey any additional information.

Additional analyses in Krakow, Kaunas and Novosibirsk adjusting for the presence of hearing, vision or other problems that might have interfered with cognitive testing did not significantly affect the results on smoking and cognitive function; these data were not collected in the Czech sample, and were thus not included in the main analysis.

Additionally, Tobit regressions of delayed recall and smoking gave nearly identical results, suggesting that potential ceiling effects did not bias simple linear regression estimates for this cognitive outcome, as previously found for alcohol.

Finally, interactions between smoking status and alcohol intake were not statistically significant for most cognitive tests, as shown graphically in Figure 4.7. A notable exception was a significant interaction term for letter search in men ($p<0.001$), suggesting that the association between smoking and letter search differs by the level of alcohol consumption. Former smokers had highest letter search scores at high and moderate levels of alcohol consumption, while never smokers had highest letter search scores at the lowest level of alcohol consumption and lower scores at higher levels of alcohol consumption. In other words, in former smokers letter search scores increased slightly with increasing alcohol consumption, whereas in never and current smokers letter search scores tended to decrease or remain similar. In men, the interaction was also borderline significant for global cognition ($p= 0.032$). Again, former smokers had better global cognitive scores at moderate and high levels of alcohol consumption than never smokers who were light drinkers (reference group).

Additionally, in women, current smokers who were also heavy drinkers had significantly lower letter search scores ($p<0.01$), compared to never smokers who were light drinkers (reference group). Overall, the interaction did not attain statistical significance (global Wald test $p=0.195$). However, the lack of statistical significance in women could reflect low power, given the low numbers of smokers and heavy drinkers in the sample. For the other cognitive tests, female heavy drinkers appeared somewhat more likely to have better cognitive scores, if they were life-long non-smokers, but again the results were not statistically significant.

Results for the interaction between smoking and drinking frequency were similar (see Figure 4.8. below). However, in the case of drinking frequency the interaction for letter search in women was statistically significant (global Wald test $p=0.007$) and borderline significant for delayed recall (global Wald test $p=0.024$) and global cognition ($p=0.016$.) In women, current

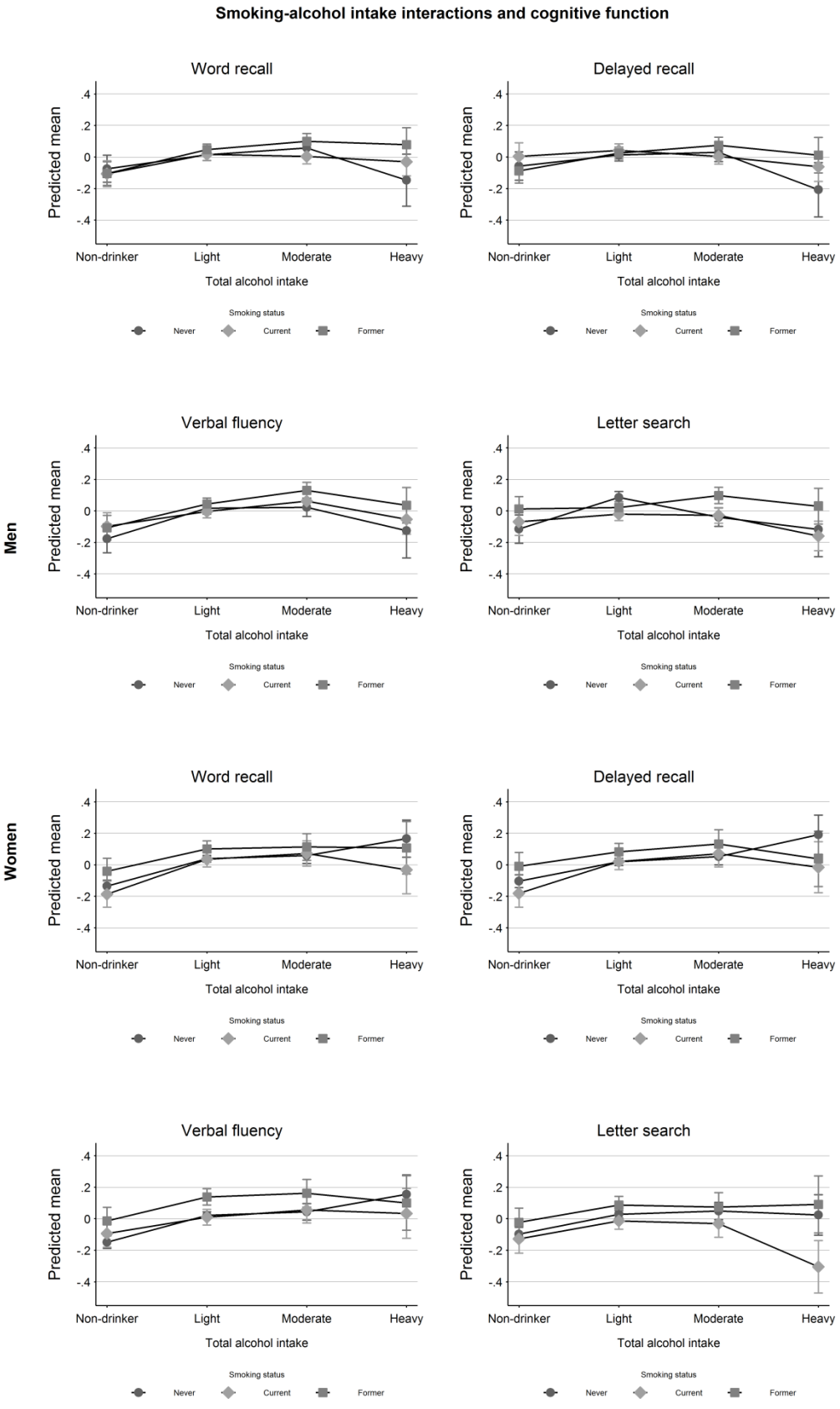

Figure 4.7. Predicted mean cognitive scores for categorical interactions between smoking status and total alcohol intake
Levels of smoking status are shown as connected symbols and levels of alcohol consumption as values on the x-axis. Regression models were adjusted for relevant covariates (age, education, assets, health measures, centre and measurement wave).

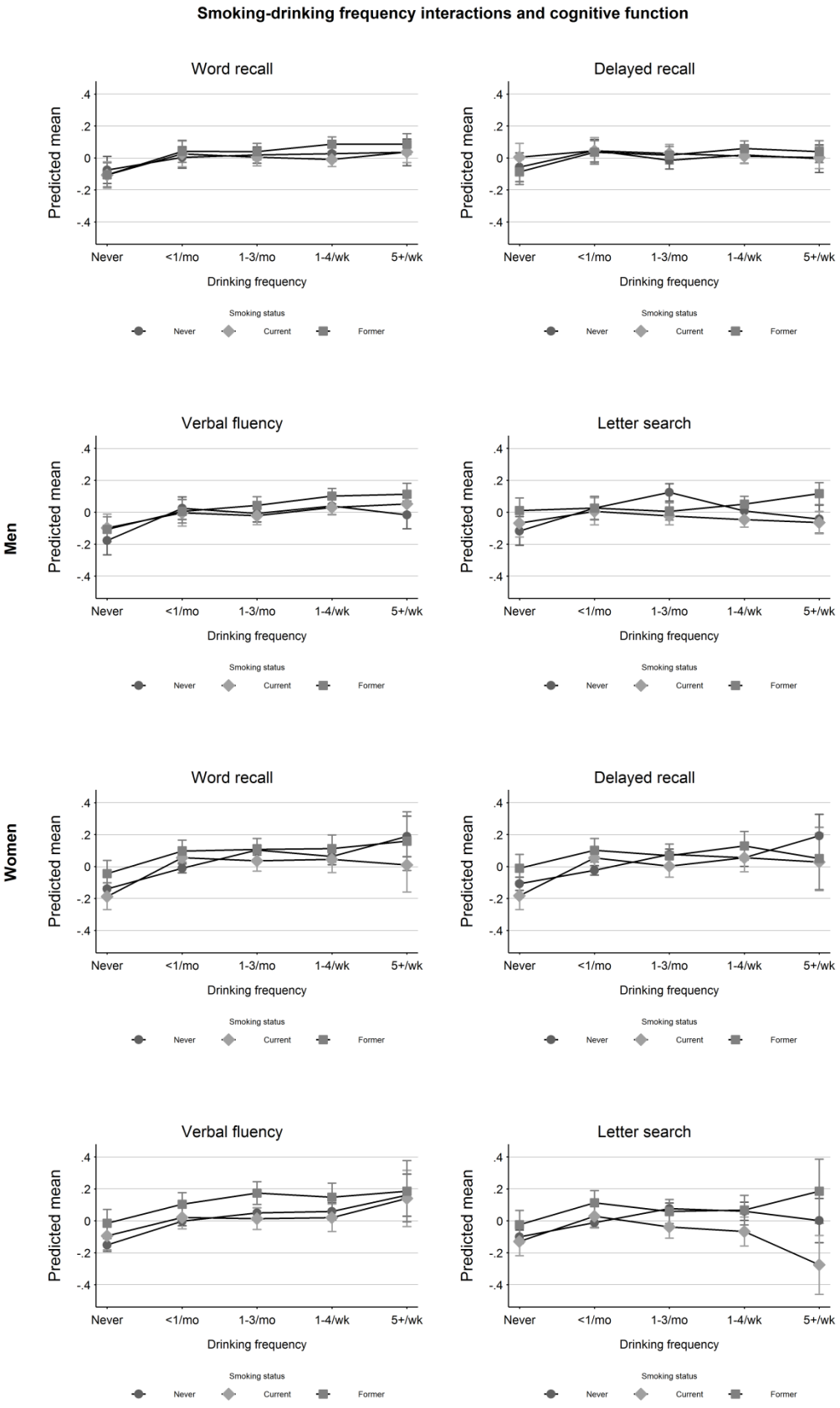

Figure 4.8. Predicted mean cognitive scores for categorical interactions between smoking status and drinking frequency
Levels of smoking status are shown as connected symbols and levels of drinking frequency as values on the x-axis. Regression models were adjusted for relevant covariates (age, education, assets, health measures, centre and measurement wave).

smokers performed worse on the mental speed test at high drinking frequencies, whereas never and former smokers tended to do better. Similarly, current smokers had lower scores on delayed recall and global cognition at higher drinking frequencies, compared to never smokers who drank occasionally (reference group).

There were also no significant interactions between smoking and binge drinking for any cognitive test. There was no evidence of heterogeneity across centres for any combination of smoking and alcohol measures (three-way interactions between smoking, alcohol and centre were not statistically significant for any cognitive test).

Chapter 5. Discussion

The results of the thesis were presented in the previous chapter. This chapter opens with a brief summary of the key findings, and then provides a discussion of limitations and strengths which are common to this work. The next three sections of this chapter follow with separate discussions of the specific results of analyses on mid to late life cognitive function with life course SEP (Section 5.3.), alcohol consumption (Section 5.4.) and smoking behaviour (Section 5.5.) as exposures of interest, respectively. The overarching implications of the findings of the thesis are then discussed. Finally, suggestions for future research are outlined in the seventh and final section of this chapter.

5.1. Summary of the findings

The key findings of the thesis can be briefly summarized in the following way. First, in these four Central and Eastern European populations, measures of SEP from across the life course were associated with cognitive function in middle and older age, similar to studies in Western populations. The direct path from own education to cognition was consistently the strongest, followed by weaker direct paths to cognition from current SEP and parental education. There was some evidence of accumulation of disadvantage and advantage across the life course, with associations between childhood SEP and cognition partly mediated by participants' attained education and, to a much lesser extent, current material circumstances. Despite these

broad similarities in the pattern of associations across centres, some significant differences between centres were also observed. Associations between current material circumstances and cognition were stronger in Novosibirsk and Krakow, particularly in men, and childhood material conditions were directly associated with cognition only in Russian women. In addition, the association between education and cognitive function was consistently strong but its magnitude varied across centres. In regression analyses adjustment for two core health behaviours, alcohol consumption and smoking, did not significantly affect the estimated associations between life course SEP measures and cognition. The associations between life course SEP and cognitive function were also not materially changed by adjustments for health measures, including self-rated health and self-reported history of physician diagnosed chronic conditions.

Second, the cross-sectional associations of measures of alcohol consumption and smoking with cognitive function were relatively weak. This may also explain the limited impact of adjustments for these behaviours on associations between life course SEP measures and cognitive function in regression analyses. Lower cognitive performance with high alcohol consumption was observed only for some conventional alcohol indices and not necessarily in both genders. Notably, in men the associations between total alcohol volume and cognitive test scores consistently showed inverse U-shaped associations. Heavy male drinkers (>40 g per day) had significantly lower scores on tests of mental speed and concentration ($p<0.01$), delayed recall ($p<0.05$) and global cognition ($p<0.01$), compared to the reference group (<10 g per day). However, total alcohol intake was generally not associated with cognitive scores in women. In women, higher drinking frequency was associated with better performance on most cognitive tests, except for a non-significant U-shaped association with the test of mental speed. In contrast, drinking frequency was generally not associated with cognitive

performance in men. Average quantity of alcohol consumed per occasion showed an inverse U-shaped relationship with most cognitive functions, particularly in women. Women drinking >60 g per occasion had significantly lower verbal fluency scores ($p<0.01$), compared to women drinking ≤25 g per occasion. However, reductions in test scores at higher quantities were less consistent in men and not significant for other cognitive tests in women. Interestingly, in this study binge drinking was not independently associated with cognitive performance, both after controlling for total alcohol intake and in stratified analysis. In addition, there was no consistent association between alcohol type and cognitive performance.

Third, in Novosibirsk, where relevant data were collected on past drinking behaviour, former drinkers who quit drinking because of poor health showed significantly worse performance on several cognitive tests, compared to current drinkers. In contrast, no significant differences in cognitive performance were observed between current drinkers and former drinkers who quit drinking for reasons not related to health. Significantly worse cognitive performance was also observed in stable non-drinkers in women, whereas only a very small number of men were classified as stable non-drinkers. The associations with cognitive function in former drinkers and stable non-drinkers were markedly attenuated after adjusting for health measures, although particularly in female stable non-drinkers they remained statistically significant. In addition, reduced use drinkers who reported drinking more in the past generally did not show systematic differences in cognitive performance compared to stable drinkers. Overall, past drinking did not seem to significantly affect the results among drinkers.

Fourth, smoking status was associated with reduced mental speed in both genders ($p<0.01$) but not with other cognitive measures. Female former smokers generally showed better cognitive performance, compared to lifelong non-smokers. Self-reported smoking history, measured by pack years, did not show a relationship with cognitive performance. Associations between smoking and cognitive function were also not systematically modified by the level of alcohol consumption, with the exception of lower scores for some cognitive tests in female smokers who were frequent drinkers, compared to female non-smokers who drank alcohol occasionally (reference group).

Finally, associations of alcohol consumption and smoking with cognitive function were largely unchanged by adjustments for other health-related behaviours and health measures (self-rated health and self-reported medical history, including history of cardiovascular disease and stroke) or by adjustments for vascular risk factors (e.g. BMI, systolic and diastolic blood pressure, resting pulse, and plasma concentrations of low and high-density lipoproteins) in additional analyses.

5.2. Limitations and strengths

This section is divided into two parts. In the first part limitations which are common to this work are discussed, followed by a discussion of overarching strengths in the second part. Limitations and strengths pertaining to specific analyses on life course SEP or core health behaviours are acknowledged in corresponding discussions in the next three sections of this chapter.

5.2.1. Limitations

Several limitations should be acknowledged when interpreting the results presented in this thesis. First, the main limitation of this thesis is its cross-sectional design, which makes it difficult to establish the direction of causality between the variables. Data on exposures and cognitive outcome variables used in the thesis were collected at a single time point and some exposure data were collected retrospectively. In absence of relevant data the possibility that the associations between selected exposures and cognitive function are partly a result of selection by prior cognitive ability into levels of exposures could not be directly examined. This study sampled middle-aged and older populations, and direct measures of childhood cognitive ability or proxy measures, such as pre-existing test results or academic records, could not be obtained. Alternatively, a measure of premorbid crystallized intelligence could be used as a proxy for peak cognitive ability. Although such measures are not a substitute for childhood cognitive ability, they can provide an estimate of premorbid intelligence or serve as a proxy for cognitive reserve because they are relatively unaffected by cognitive decline. Tests of current reading ability, such as the National Adult Reading Test (264), which take advantage of language-specific pronunciation properties, are frequently used to measure premorbid intelligence in population studies. However, relatively little effort has gone into developing and evaluating performance of comparable instruments in Central and Eastern European populations. The focus of the HAPIEE study was on ageing and, accordingly, age and morbidity sensitive measures of cognitive function were collected.

In addition to possible selection by prior cognitive ability, another potential source of reverse causality, which cannot be excluded, is related to change in circumstances or behaviour as a result of poor cognitive status or cognitive decline. For example, low cognitive scores in non-

drinkers could reflect poor vascular health or cognitive problems related to past alcohol abuse, which was the catalyst for quitting drinking. Issues related to reserve causality are discussed further in subsequent sections pertaining to specific results on SEP and health behaviours. Finally, cross-sectional associations may not be reproduced in longitudinal studies of cognitive decline, as suggested, for example, by longitudinal studies with longer follow-ups failing to confirm an association between education and cognitive decline (16,140), previously reported in cross-sectional studies and studies with relatively short follow-up periods.

In an attempt to overcome some of the limitations of cross-sectional design, associations of selected exposures at baseline with cognitive change were analysed in a subsample of participants with repeated cognitive measures (n=8,193). However, these analyses had limitations of their own. The re-test interval was relatively short, 3.5 ± 0.7 years on average. Improvement in mean cognitive scores observed for most tests between the two assessments suggested that the interval was too short to detect a decline in cognitive function and that significant practice effects were present. Problems of statistical estimation associated with practice effects and regression to the mean are likely to be amplified over such a short re-test interval. Three or more time points are preferred for longitudinal studies, and limitations of modelling change with only two time points are well known (265). One of the issues encountered in analyses of cognitive change was whether to include adjustment for baseline values of the outcome measure. Baseline adjustment can introduce spurious associations, and has been suggested to be inappropriate in analyses of cognitive change and its associations with SEP measures (266,267). In fact, results of analyses of cognitive change appeared to be biased by baseline adjustment, particularly for education. Because of these limitations of

analyses of cognitive change, it was decided that cross-sectional results were more informative and should be the main focus of the thesis.

Second, baseline cognitive data were incomplete in three (Czech towns, Novosibirsk, and Krakow) of the four study centres because only a subsample of participants were eligible for cognitive examination at baseline in these three centres. Thus, missing data for cognition in the three original centres were generated by a combination of missing by design, since cognitive function was assessed only in a subset of participants at baseline, and longitudinal attrition because some of the participants who were not eligible for cognitive assessment at baseline were subsequently lost to follow-up. Participants with lower baseline cognitive scores had a higher chance of attrition ($p<0.001$), a pattern commonly observed in cognitive ageing studies (268,269). This pattern is likely to apply to participants who were not eligible to participate at baseline cognitive assessment and were subsequently lost to follow-up. In contrast, there were very little missing data in Kaunas (under 4% after listwise deletion on all variables in regression analyses). However, additional analyses in the three original centres restricted to participants who had baseline cognitive data but were lost to follow-up generally gave very similar results to analyses in participants who remained in the study. This suggests that attrition is unlikely to affect the overall patterns of associations presented in this work.

In this thesis, missing data were handled in two ways: 1.) by pairwise deletion (whereby participants with partial data could be included; this is the default for the WLSMV estimation method) in structural equation analysis and 2.) listwise deletion (whereby only participants with complete data are included) in regression analyses. Methods that make use of missing data are usually more efficient than complete case analysis and WLSMV with pairwise present has been shown to yield consistent parameter estimates and standard errors under

particular variants of MAR assumption (whereby missingness is assumed to be a function of covariates, if the model contains any) (262). Full-information maximum likelihood (FIML), another commonly used method for dealing with missing data in structural equation modelling, is generally considered superior (more efficient and unbiased under MAR) to pairwise present (270) but is not suitable for models with categorical outcomes or mediating variables and thus could not be used in this thesis.

Regression analyses in this thesis used listwise deletion, which assumes that the data are MCAR. This assumption is unlikely to be tenable in practice and examination of missing data patterns suggested that it may also not be tenable in this study, as previously discussed in the section on missing data on pg. 94, although the extent (and indeed direction) to which this may have biased the results remains unknown. In addition, handling of missing data by listwise deletion inevitably resulted in loss of power and precision in regression analyses because the proportion of missing data in the tree original centres was considerable. Thus, handling of missing data by listwise deletion in regression analyses may be considered a limitation.

In the context of this thesis, multiple imputation would offer a possible alternative for dealing with missing data which could be applied to both structural equation modelling and regression analyses. Under missing at random mechanisms, multiple imputation is more likely to result in unbiased estimates than complete case analysis (271). However, while multiple imputation tends to have negligible bias and listwise deletion tends to be biased under MAR mechanisms, a less acknowledged fact is that there are other mechanisms under which complete case analysis has negligible bias and multiple imputation is biased (271). Multiple imputation is now readily available in most commercial statistical software.

However, under complex scenarios with relatively large proportions of missing data multiple imputation is a time consuming process because it is a computationally-intensive method. In this thesis, missing data patterns were relatively complex, proportion of missing data relatively high, optimal imputation models would be relatively complicated with a large number of categorical and non-normally distributed variables and group-specific imputations would be required (272). These challenges are not insurmountable but they limited the feasibility of multiple imputation within the scope and time-constraints of this thesis. The sensitivity analyses suggested that attrition was unlikely to affect the overall patterns of associations presented in this work; this supports the view that, despite the limitations of complete case analysis, handling missing data by multiple imputation would be unlikely to change the conclusions of this thesis.

Although multiple imputation is generally believed to be more efficient and may be less biased than listwise or pairwise deletion, it still assumes that the data are missing at random. Where the data are suspected to be missing not at random, and this could plausibly be the case in this thesis, multiple imputation offers no advantage over other methods for dealing with missing data. Sensitivity analysis may be used to examine whether conclusions are sensitive to plausible MNAR mechanisms but, as observed by Carpenter and Kenward (273), methods for sensitivity analysis are usually problem-specific. They suggest a more formal alternative approach by conducting standard multiple imputations assuming MAR, thereby obtaining parameter estimates for each imputed data set. A weighted average of these parameter estimates is then used to obtain a MNAR parameter estimate, with the weights reflecting the assumed degree of departure from MAR. Contextual knowledge may inform the choice of weights and, additionally, a selection model may be specified, which explicitly models the probability of observing the data. Although it is beyond the scope of this thesis,

this approach may prove accessible for future research in the field of cognitive ageing. In the end, it is worth bearing in mind that any method for handling missing data is only as good as its underlying models and assumptions, some of which are inherently untestable, calling for careful consideration of plausible missingness mechanisms and contextual knowledge.

Third, the results of this thesis pertain to specific urban populations, not countries and this limits the generalizability of the findings. There are significant differences in health and socioeconomic indicators between urban and rural areas in these countries. For example, significant differentials exist in smoking rates between urban and rural areas in these countries, especially among women (274–276). The participating towns and cities may also not be entirely representative of urban populations in the respective countries. Educational levels were higher in large cities than in smaller towns. The relatively low educational level in the Czech sample may be partly explained by differences in the degree of urbanisation (the largest Czech town had a population of about 100,000 people, whereas Novosibirsk, Krakow and Kaunas are important regional centres) (83). Despite this, levels and trends in socioeconomic indicators and mortality in the participating towns and cities are similar to their respective countries, and it is very likely that these study samples broadly reflect the situation in their countries' urban populations.

Fourth, achieving satisfactory response rates was one of the main challenges of the study, and systematic non-participation could bias the results. A survey conducted in a sample of non-respondents suggested that participants in this study were healthier and wealthier than the general populations from which they were drawn (251). A non-response rate of 20-40% and overrepresentation of wealthier and healthier individuals among responders are common in epidemiological studies in industrialised countries (255). Low response and differences in

characteristics between responders and non-responders are often taken to indicate nonresponse bias, although nonresponse bias of effect measures is not a logical consequence of low response (277). For example, as shown by several studies, overrepresentation of lower socioeconomic groups and less healthy individuals among non-responders need not result in biased estimates of associations, and relative social class differences in health outcomes may still be similar among responders and non-responders (277–280). Possible implications of attrition and non-response for individual analyses presented in this thesis are discussed further in subsequent sections.

Fifth, exposure measures and covariates used in this work are largely based on self-reports. Although reliability and validity of self-reported measures used in this thesis are generally believed to be adequate, they are likely to be less accurate than objective measures. Self-reported measures are error prone and, more importantly, may be subject to systematic reporting bias. For example, socially undesirable and desirable characteristics or behaviours are likely to be underreported and overreported. Reporting accuracy depends on the attributes of the measures as well as contextual factors and respondent characteristics. Possible implications of using self-reported measures of life course SEP, alcohol and smoking are developed in more detail in subsequent sections. Regarding the covariates used in this thesis, in validation studies (281–286) reporting accuracy for the various self-reported chronic conditions was mostly moderate-to-high but varied significantly between studies and across conditions. Measures of self-reported chronic conditions were supplemented by objective measures of vascular risk factors used as covariates in additional analyses, although in the three original centres current measures of vascular risk factors were not available for all participants.

Sixth, potential limitations of using cognitive scores standardized using centre-specific means and standard deviations for each test as the outcome should also be considered. By using centre-specific standardized cognitive scores participants from different centres with the same z-scores share the same relative position within the distribution but not the same absolute score. A limitation of using centre-specific standardized cognitive scores rather than standardizing using whole population means and standard deviations or, alternatively, means and standard deviations of a reference group is that it may limit direct comparisons across populations, if means and standard deviations differ significantly from one centre to another (287). In contrast, one possible advantage of using centre-specific standardized scores is that the true or theoretically relevant metric may be relative to the distribution of a given subgroup or population and thus group-specific standardized scores may better reflect true parameters (287).

For example, given the differences in methodology (in-home assessment vs. clinic) a high-scoring Novosibirsk participant may be more appropriately compared to a high-scoring Krakow participant than a Novosibirsk participant whose absolute score (and consequently corresponding z-score standardized using the same transformation across groups) is the same but not actually equivalent in Novosibirsk terms.

In this thesis, empirical consequences, both negative and positive, of using centre-specific standardized cognitive scores may be limited since there was a very high level of agreement between the results of regression analyses with cognitive scores standardized using whole sample means and standard deviations as outcomes and results from regression analyses with centre-specific standardized cognitive scores as outcome measures. However, this may not

generalize to other contexts and, depending on the application, standardization with regard to whole sample or reference group mean and standard deviation may be more appropriate.

Finally, other limitations or particular implications of the limitations listed above pertaining only to specific analyses on life course SEP or the two core health behaviours, alcohol consumption and smoking, are expanded upon in subsequent sections, which discuss in some detail the findings on each exposure.

5.2.2. Strengths

The limitations of this thesis are balanced by its overarching strengths. First, this work is one of the first, and certainly the most comprehensive, study of socioeconomic and lifestyle correlates of cognitive ageing in Central and Eastern European populations. It uses data from one of the largest prospective epidemiological studies of middle-aged and older populations ever conducted in Central and Eastern Europe and is based on random population samples. This type of individual-level data, based on random samples, is still not widely available in Central and Eastern Europe, and perhaps one of the main reasons why cognitive ageing, or healthy ageing in general, remains understudied in this region. Since Central and Eastern Europe differs in many respects from Western countries, this likely to be an important omission. Compared to Western Europe, the higher mortality in Central and Eastern Europe, particularly the FSU countries, reflects a high cardiovascular disease burden, with significant contributions from alcohol and smoking (65). Healthy life expectancy at older ages also appears to be lower (78), and greater declines with age in healthy life expectancy (80) as well as cognitive (81) and physical functioning (82) have been observed in some Eastern

European populations. In addition, the region is unusual in having undergone two unique types of social change over the past seventy years, resulting in dramatic increases in income inequality after several decades of relative equality (85). Also, the CEE countries, which saw the most dramatic increases in income inequality, are generally the countries, which experienced the most pronounced deterioration in health and life expectancy during the economic transition.

Second, this work was able to take advantage of relatively good data on cognitive function. Cognitive function was measured using a test battery comprised of four neuropsychological tests of multiple cognitive domains, generally administered in controlled conditions by specially trained personnel. The cognitive measures used are sensitive to ageing and morbidity. In addition, the cognitive tests were used to derive global measures of cognition, which account for or limit the extent of measurement error.

Third, assessment of exposures (life course SEP, alcohol consumption and smoking) was relatively detailed and included current as well as retrospective measures. In addition, analyses were adjusted for a range of potential confounders and some relevant mediators and additional analyses were conducted with further adjustments for cardiovascular risk factors measured at baseline clinical examination.

Fourth, where combining data from the four centres was appropriate, the high statistical power of the pooled sample represents an obvious advantage. For example, exposures which are not very common at the population level in middle-aged and older participants, such as heavy or binge drinking, could thus be studied more readily.

5.3. Life course SEP and cognitive function

This section discusses the results of analyses on life course SEP and mid to late life cognitive function, presented in Section 4.2. of Chapter 4.

This study in four Central and Eastern European population samples suggests that in these populations cognitive function in mid and later life reflects the influence of SEP at several stages of the life course (childhood, young adulthood and middle or older age), similar to studies in the West. The strongest path to cognition was from education, a weaker path was observed from current SEP (approximated by household asset ownership), and a generally significant but modest direct path connected mother's education and cognition. A considerable proportion of the total effect of mother's education on cognition was indirect, mediated by participants' attained education and, to a lesser degree, current asset ownership. In contrast, participants' education had only a very small indirect effect on cognition transmitted through household assets. The pattern of results was broadly similar, albeit with some differences, across study centres.

The results of this study should be interpreted in the context of its specific limitations, in addition to those discussed in the previous section. First, the study had a cross-sectional design and childhood SEP measures were reported retrospectively. Retrospective reports are vulnerable to recall bias and misclassification. Assuming non-differential misclassification, this would likely result in the associations being underestimated but the possibility that reporting accuracy is affected by cognitive status cannot be ruled out. If misclassification was differential because childhood conditions were reported less accurately by participants with

poorer cognitive function, this could lead to either an overestimation or underestimation of the association between childhood SEP and cognition. However, participants were still relatively young (average age of the sample was 60 years), and significant reporting bias due to cognitive impairment seems unlikely. It has also been shown that reporting accuracy for simple socio-demographic information is still reasonably high in old age (288). Additional sensitivity analyses confirmed that measurement error would not change the conclusions regarding the role of childhood SEP measures and, additionally, current household assets. Moreover, some studies suggested that adjustment for misclassification in predictor variables with relatively few categories may not necessarily have a large effect on coefficient sizes (289).

Second, the categorization adopted to achieve comparability of education across centres resulted in some loss of information and may have introduced some potential for misclassification of participants' educational level. However, sensitivity analyses suggested that alternative classifications of educational categories did not dramatically change the associations involving education or their ordering across centres. In this study, education was interpreted as a measure of participants' SEP in young adulthood. Although the majority of participants in all centres reported completing full-time education in young adulthood, some participants may have attained additional formal qualifications later through part-time or evening study. However, this is unlikely to change the nature of association between education and cognitive function. Cognition is most strongly associated with formal education obtained in young adulthood, while cognitive (147) and economic (290) returns to adult qualifications may be less substantial. Thus, if significant numbers of participants attained their highest formal qualification after completing full-time education the associations would probably be an underestimate.

Third, given the incomplete baseline cognitive data in three of the four study centres, participants with missing data on cognitive function were younger, more likely to be male, had lower educational attainment, higher childhood SEP, and owned fewer assets than those with cognitive data. However, this is unlikely to bias the estimates of the associations between SEP and cognition. Like respondents with lower baseline cognitive function, respondents with lower baseline scores on SEP measures also had a higher chance of attrition. However, additional analyses in participants who had baseline cognitive data but were lost to follow-up gave similar results to analyses in participants who remained in the study. Attrition is, therefore, unlikely to introduce a major bias.

Fourth, another important limitation associated with cross-sectional design is the challenge of reverse causality, in absence of a measure of prior cognitive ability. Two studies that were able to adjust for childhood or adolescent cognitive ability observed significant independent effects of education and adult social class, and a fully or largely indirect effect of childhood SEP on midlife cognition mediated by prior ability and later SEP (126,127); in another study, only childhood cognitive ability and education were associated with cognition in old age (128). Thus, the structural effects of life course SEP on cognition may have been overestimated in this study. In addition, no relevant data were available to investigate the issue of reverse causality, although both social selection and causation mechanisms are likely to be important in generating the associations. For example, education has been shown to enhance adult fluid cognitive function over and above significant ability-based selection into education (144).

Finally, estimation of direct and indirect effects in mediation analysis assumes there is no unmeasured confounding of the exposure-outcome, mediator-outcome and exposure-mediator

relationships (291). Specification of the model and selection of covariates was based on substantive knowledge and results from preliminary regression analyses but residual confounding remains a possibility. Thus, any conclusions should be drawn cautiously.

Despite the limitations, this is the first study of life course SEP and cognition in middle and older age in Central and Eastern European populations. Among the strengths of this study are a large population-based multi-centre sample with objective verbal and non-verbal neuropsychological measures and relatively good data on SEP.

Several findings deserve a comment. The direct path from education to cognition was consistently strong, especially relative to other SEP measures, confirming the education-cognition relationship found previously (15,131,135). This may owe to mental stimulation provided by education with potentially lasting benefits for cognitive reserve. In addition, education also fosters development of non-cognitive skills, such as motivation, self-regulation and autonomy, which are important for success and well-being in adulthood and later life (42). Beyond direct influences on cognition, education is a significant determinant of occupational status with implications for cognitive ageing. This aspect was especially important in credential-based labour markets typical of communist societies. Educational qualifications were the main basis for labour allocation and the main route to professional occupations, resulting in stronger associations between education and occupation than in Western countries (292). However, education was only weakly correlated with higher incomes and material inequalities may have been less important in mediating the association between education and cognitive health.

Another plausible contributing explanation for the strong education-cognition link in these societies is related to communist regimes' efforts to create a greater equality of educational opportunity, especially in favour of children from disadvantaged socioeconomic backgrounds. Consequently, ability-based selection into education may have increased in importance relative to family background (293), resulting in a high correlation between educational attainment and cognitive ability.

Some reductions in social origin-based educational inequality were generally achieved, most likely as a result of educational expansion (103,105). The most dramatic reductions in educational inequality occurred in the immediate post-war period with inequalities starting to rise again in the 1970s (101,102). Despite the regimes' efforts, parents' social position remained a significant determinant of offspring's educational chances throughout the period, possibly even stronger than in Western countries (105). In socialist countries educational expansion and industrialization rather than egalitarian policies were apparently the most significant forces shaping educational inequality during communism (100–103,105). While these trends are common to all Central and Eastern European countries, country differences in these processes would be expected depending on the national historic and institutional contexts. For example, Central European countries inherited a stronger vocational orientation in secondary education, which is associated with greater inequality, compared to the Soviet Union (294). Moreover, egalitarian policies, especially those directly aimed at improving educational access of children from disadvantaged backgrounds, were not always systematically pursued. In Soviet Russia pressures created by the rapid expansion of secondary schooling actually inadvertently increased inequality in access to higher education (101). Such intraregional variation in the interplay of contextual factors may go some way in

explaining the differences in magnitude of the education-cognition association across centres in this study.

A generally significant association of currently owned household assets with cognition was observed, particularly in Novosibirsk and Krakow, pointing to the potential importance of material circumstances for mid-late life cognition in these populations. Previous studies have reported an independent association of cognition with income and wealth (122,131,135,173). In post-Soviet Russia, with widening income (95) and health (60) inequalities, material circumstances may have become more prominent in determination of health compared to other post-communist countries, such as the Czech Republic, where this trend has been less apparent.

Mother's education showed a significant direct path to cognition in all but one study centre, where it showed only an indirect path to cognition mediated by participants' own SEP. Several earlier studies used only paternal measures (123,126–128) but previous research which used measures from both parents generally found a stronger association between mother's education and mid to late life cognition, compared to paternal measures (121,122). For example, in a cohort of Finnish middle-aged men only mother's education was directly associated with cognition; the association with father's occupation was entirely mediated by participant's own SEP, while mother's occupation and father's education were not important for midlife cognition (121). In another study, father's occupation was associated with late life cognition through cognitive development, while father's education and material circumstances were not (128). Thus, among childhood SEP measures father's occupation (123,126–128) and, as in this study, mother's education (121,122) appear to be especially important for mid to late life cognition. However, with rising female employment and

changing gender roles this may change in future cohorts. Given the rapid educational expansion and removal of gender inequalities in education under socialism (105), rising levels of women's education over the period may have a positive impact on cognitive ageing not just in the more recent cohorts of women but also in the future generations of men and women.

On the other hand, significant path from childhood amenities to cognition was observed only in Russian women. The latter observation might reflect the greater degree of material disadvantage experienced by Russian cohorts in childhood (295). Childhood conditions were found to be strongly associated with cognitive impairment in oldest old Chinese, where severe childhood adversity was common (176). It has previously been found that Russians who were born before or during WWII were shorter than those born later, after controlling for secular trend (296). It is plausible that childhood conditions of these participants affected not only their height but also their cognition in later life, although in the latter case the effect on global cognition was only significant in women.

In addition to the main findings on cognitive function, the associations between various SEP measures also deserve a comment. In the light of increasing economic returns to education reported in the region since the onset of transition (97), the finding of a moderate effect of education on current asset ownership in these relatively recent (post-1990) data may be important. The results are also consistent with recent findings on intraregional variation in economic returns to education, which were found to be high in Poland, medium in Russia and low in the Czech Republic (297). The effect of education on current material circumstances was somewhat stronger in men than in women. The indirect effect of education on cognition through its association with household asset ownership was rather weak,

although it was stronger in Novosibirsk and Krakow, particularly in men, than in the other two centres, owing to stronger associations of current material circumstances with cognition or education or both in these centres.

Significant tracking of SEP over the life course was observed in all these post-communist countries. Mother's (and father's) education had a notable influence on participants' educational attainment, whereas the effect of childhood material conditions was less important. In societies where opportunities for accumulation and intergenerational transmission of wealth were limited, family cultural capital embodied in parents' education may have been especially important for offspring's educational attainment (108). Both childhood SEP measures also had small independent effects on current material circumstances. These paths, particularly those involving participants' education, were important in mediating the associations between parental education and childhood material conditions and cognition later in life. This indicates a degree of accumulation of childhood social disadvantage and advantage on cognitive function across the life course, consistent with previous studies in these populations showing considerable tracking of social disadvantage and advantage, with a cumulative effect on self-rated health (298) and depression (299). However, these findings are based on data collected after the fall of communism and, to some extent, probably also partly reflect the effects of economic transition. At least in Russia, the association between parental and adult socioeconomic position may have actually strengthened as a result of economic transition (300).

In the Warsaw study of children born in the 1960s, the association between parental social background and childhood cognitive ability was, contrary to authors' expectations, at least as strong, if not stronger, as in the West, despite the relative absence of educational, health care

and community divisions typically associated with socioeconomic position (301). The present study, in four urban populations in Central and Eastern Europe, confirms that the influence of life course socioeconomic trajectory is still reflected in cognitive function in midlife and beyond, similar to Western populations. This suggests a largely universal structure of associations between SEP across the life course and cognition in later life. In addition to the differences between CEE and Western countries, there are also significant differences between these populations. Unlike the Russian Federation, the Czech Republic, Poland and Lithuania had a capitalist economic system before the WWII, which was still in living memory. In addition, Czechoslovakia was a hardline communist state until 1989 with a commitment to a centrally planned economy and no legalised private employment, whereas decentralisation begun about a decade earlier in Poland as the regime came under Solidarity-led pressure (93). With this in mind, the similarities between these populations are all the more remarkable.

However, the presence of significant differences in associations between life course SEP and cognition between centres suggests that contextual factors may also have played a role. For example, the stronger effect of material circumstances in Novosibirsk, both in childhood and in adulthood, may reflect the harsh living conditions in the past and rapidly growing income inequalities during post-communist transition. In addition, the association between education and cognitive function in these cohorts was consistently strong but differences in the magnitude of this association varied between centres. It is possible that this variation partly resulted from differences in national histories and institutional settings, which may have affected the structure of the educational system, degree of educational inequality and the strength of ability-based selection into education. On the other hand, some of these

differences probably occurred by chance and caution is required before accepting the interpretation of these differences as effects of contextual factors.

Finally, one further and somewhat unexpected finding that is worthy of mention is that neither alcohol consumption nor smoking appeared to notably mediate the associations between any of the life course SEP measures and cognitive function in preliminary regression analyses. In regression analyses of cognitive function the coefficients for SEP measures remained largely unchanged after adjusting for alcohol intake and smoking status. Consequently, there was little justification for including measures of alcohol consumption and smoking in structural equation models of life course SEP and cognition. Possible reasons for the apparent lack of significant mediation of the associations between SEP and cognition by alcohol consumption and smoking in these four Central and Eastern European populations will become evident in the next three sections.

5.4. Alcohol consumption and cognitive function

Positive associations were observed between life course SEP measures and cognitive function but results from preliminary analyses suggested that these associations were not significantly explained by adjustments for two core health behaviours, alcohol consumption and smoking. This section discusses the results of separate analyses on alcohol consumption and mid to late life cognitive function, presented in Section 4.3. of Chapter 4. Alcohol consumption is significantly associated with premature mortality and cardiovascular disease in Central and Eastern Europe, particularly in FSU countries, and is, therefore, potentially important for cognitive functioning in these countries.

In this large study in four Central and Eastern European populations with high prevalence of binge drinking, some evidence was found for an inverse U-shaped relationship between total alcohol intake and cognitive function in men and average quantity of alcohol consumed per occasion and cognitive function in women. However, consistent with Richards et al. (196), in women for total alcohol intake this pattern was only seen for the test of mental speed; for all other cognitive measures, cognitive scores were not lowest in the highest drinking category. Similarly, in men the inverse U-shaped association between average quantity of alcohol consumed per occasion and cognitive scores was weaker and less consistent than for total alcohol intake. Drinking frequency was generally not associated with cognitive function in men, while it showed a linear positive association in women. Binge drinking and alcohol type were not associated with cognitive performance after stratification or adjustment for total alcohol volume. In Novosibirsk, former drinkers who quit drinking because of poor health and female stable non-drinkers had significantly lower cognitive scores for several cognitive

tests (immediate and delayed recall and global cognition) and non-significantly lower scores for the remaining tests, compared to current drinkers. No systematic differences in cognitive performance were observed between stable drinkers and reduced use drinkers in this centre. Echoing the results from all centres, there were some small improvements in cognitive scores at moderate intakes and lower letter search scores were observed in heavy male drinkers but other than this the associations between alcohol consumption and cognitive function in Novosibirsk were modest.

In addition to the general limitations of this thesis, some specific points should be considered when interpreting the results of this study. First, given the difficulty of establishing causality in a cross-sectional design, the association between cognitive function and alcohol may be partly explained by the influence of prior cognitive ability and socioeconomic position on alcohol use (233,234). High alcohol consumption and high risk drinking pattern may be more common among individuals with lower initial cognitive ability or disadvantaged socioeconomic position, whereas higher cognitive ability and advantaged socioeconomic position are thought to be associated with moderate alcohol use. Similarly, moderate alcohol use may reflect generally moderate lifestyles, which may protect from cognitive decline.

Second, alcohol consumption measured at a single point in time may not fully capture the consequences of prolonged heavy alcohol use or account for changes in drinking patterns across the life course. Heavy drinkers may be more likely to decrease their alcohol consumption because of health-related problems, but it was not possible to comprehensively examine change in alcohol consumption patterns over the life course or distinguish former drinkers from lifelong abstainers in all centres. However, the findings from Novosibirsk, where participants were asked about their past drinking behaviour, suggest that cognitive

performance is worse in former drinkers who quit drinking because of health-related reasons, compared to current drinkers. In contrast, former drinkers who quit drinking for reasons unrelated to health did not show significant differences in cognitive performance. In addition, in all centres current non-drinkers at follow-up were asked whether they had always abstained or alternatively, why they stopped drinking. Across centres, reasons related to poor health were among the most common reasons given for quitting drinking. Thus, the difference between the reference group and non-drinkers observed in this study may be partly attributable to misclassification of former drinkers with poor health among current non-drinkers. Adjustment for basic health status measures attenuated but not always eliminated the negative association with cognitive scores in former drinkers in Novosibirsk, suggesting that residual confounding may be an additional problem in studies comparing drinkers with current non-drinkers (237). Given the poor health and lower cognitive scores observed among former drinkers, light or infrequent drinkers were used as the baseline reference category throughout this study.

Potential for misclassification is not limited to non-drinkers, since those classified as current light or moderate drinkers may have drank more in the past or reduced their alcohol consumption during the year leading up to the survey. However, in Novosibirsk, at least, no systematic differences were observed across cognitive tests between stable drinkers and reduced use drinkers. In addition, excluding reduced use drinkers from the analysis did not change the conclusions of the study. It is therefore unlikely that reverse causation bias affected the findings in drinkers.

Third, surveys of self-reported alcohol consumption are known to underestimate alcohol intake (302). However, in this study high alcohol consumption is common and public

drunkenness is not associated with social stigma in men in these countries but drinking is considered inappropriate for women, particularly in Russia (303). For example, a population survey in Russian Republic of Karelia suggested that underreporting of alcohol intake by women may be greater than for men (304). This could have introduced potentially important misclassification of alcohol consumption indices in women, while for men this seems unlikely, and may partly explain the inconsistency of results between men and women, especially at higher levels of alcohol consumption.

Finally, attrition at follow-up was significantly higher in abstainers and participants with higher drinking frequency at baseline, and participants who did not attend the re-examination clinic had lower baseline cognitive scores. Sensitivity analyses in participants with baseline cognitive data, who were lost to follow-up, generally gave a similar pattern of results to analyses in participants who remained in the study (see Appendix VIII, pg. 261). However, at higher levels of alcohol consumption participants who dropped out often had better cognitive function than participants who remained in the study, suggesting that these associations may have been somewhat overestimated, assuming this pattern also applies to participants without cognitive measurement.

A major advantage of the present study on alcohol consumption and mid to late life cognitive function is the high statistical power of the pooled sample. In addition, the measures used included multiple neuropsychological tests and detailed data on alcohol consumption, including quantity and frequency measures, and drinking pattern.

This is one of the first and certainly the largest study of alcohol consumption and cognitive function in middle-aged and older persons in Central and Eastern Europe. The most

comprehensive meta-analysis to date (186) observed a notable absence of such studies in Central and Eastern Europe, despite an increasing recognition of alcohol misuse as a significant factor in the burden of ill-health and premature mortality in these countries (20), making this study all the more important. In addition, thus far few cognitive ageing studies have focused on high alcohol consumption and drinking patterns.

In men, alcohol intake generally showed an inverted U-shaped association with cognitive performance, whereas in women drinking frequency showed a near-linear positive association with verbal cognitive scores. These results are similar to those from the 1946 British birth cohort, studied by Richards et al. (2005) (196). The authors observed an inverted U-shaped trend in cognitive scores in men, whereas in women drinkers had higher memory scores, irrespective of amount consumed, compared with abstainers, but worse baseline performance and greater decline on the letter search task across alcohol consumption categories. In addition, previous studies have shown moderate alcohol consumption to be associated with better cognitive performance or reduced cognitive risk, compared to non-drinking (189–194,305); in the largest meta-analysis to date (186), low-to-moderate alcohol consumption was associated with better cognitive test scores than non-drinking in over half the studies, whereas heavy drinking was associated with non-significantly increased cognitive risk.

In men, (mostly non-significant) worsening of cognitive scores was observed in heavy drinkers compared to light and moderate drinkers for total alcohol intake and, to a lesser extent, quantity per occasion. However, the cut-off for high alcohol intake at which a decrease in cognitive performance was detected in men (>40 g of ethanol per day) is lower than in some other studies (188,193,306), although it is still considerably higher than the limit

recommended by the WHO (307) and most safe drinking guidelines. In women, worsening of cognitive scores at high levels of alcohol consumption was observed only for quantity of alcohol consumed per occasion but not for total alcohol intake or drinking frequency, with the exception of mental speed. This may be due to lower statistical power in women for these measures. Despite the large sample size, average alcohol consumption and the proportion of heavy drinkers among women in this study were low. However, lower cognitive scores were observed in women drinking more than 60 g of ethanol per occasion, especially for the verbal measures. The striking gender gap observed in alcohol consumption is consistent with other studies in the region (205,303). Similar to this investigation, several studies have previously failed to find an increased cognitive risk among women with high alcohol consumption or found a positive association between drinking and cognitive performance (188,196,233,308).

One plausible mechanism which would explain the observed associations between alcohol consumption and cognitive function involves effects on the cardiovascular system. This echoes the "vascular hypothesis" in cognitive ageing, which suggests that vascular diseases, as well as vascular risk factors, affect not just the heart but also the brain, and through their effects on the brain affect specific cognitive functions (179). The inverse U-shaped curve for cognitive impairment is analogous to the association for cardiovascular diseases; the harmful effects of heavy drinking could partly result from increased cardiovascular risk (215,309,310), whereas better cognitive scores in moderate drinkers may be mediated by cardioprotective effects of moderate alcohol consumption (216). Consistent with Richards et al. (2005) (196), adjustments for history of cardiovascular disease and vascular risk factors in additional analyses, did not fully explain the associations between alcohol and cognitive function observed in this thesis.

Another plausible mechanism involves direct effects of alcohol on the central nervous system. Experimental studies identified direct neuroprotective action of moderate alcohol exposure, including facilitation of anti-inflammatory processes in the brain and protection against ischemia through preconditioning phenomena in neurons (216,229). In contrast, chronic heavy alcohol consumption is associated with structural and functional brain damage, such as brain atrophy (230) and loss of white matter (231). Other than from direct neurotoxic effects of ethanol, negative effects of heavy drinking could also result from alcohol-related nutritional deficiency (232).

On the other hand, the association between (moderate) alcohol consumption and cognitive function may reflect confounding by more advantaged socioeconomic position, higher initial cognitive ability and healthier lifestyles, which are more common in moderate drinkers (233,234). In fact, a recent Mendelian randomization study in Chinese individuals (238) and an unpublished Mendelian randomization study, using data from the HAPIEE study, the Whitehall II study and ELSA, found no association between moderate alcohol consumption and cognitive function, further suggesting that the association may be largely driven by selection, and socioeconomic and lifestyle factors. However, one limitation of both of these studies is that they did not include (238) or specifically examine heavy drinkers, whereas the latter also had low power.

Additionally, in the Novosibirsk study, former drinkers who quit drinking because of poor health but not former drinkers who quit drinking because of reasons unrelated to health had significantly lower cognitive scores, compared to light or stable drinkers. This confirms the view that in studies comparing drinkers with non-drinkers, misclassification of former drinkers with poor health among non-drinkers may have biased the association between

alcohol consumption and cognitive function insofar as the health differences between drinkers and non-drinkers were not adequately controlled for (237). Significantly lower cognitive scores were also observed in Novosibirsk female stable non-drinkers, whereas in men this category was too small to draw definite conclusions. Poor health may also partly explain the lower scores in this group. It is possible that the group still contains some former drinkers. Moreover, a recent study found that the presence of persistent longstanding illness significantly increases the chance of remaining an abstainer throughout adulthood (311), whereas abstention for ideological reasons, unrelated to illness or low SEP, does not appear to be associated with increased risk of poorer health outcomes, compared to drinkers (312). In contrast, systematic differences in cognitive performance were generally not observed between stable drinkers and reduced use drinkers and excluding reduced use drinkers from the analysis did not appreciably change the results for most cognitive measures.

Very few studies have examined the link between cognitive function and binge drinking in addition to quantity and frequency measures of alcohol consumption. Only two previous reports were identified that investigated the association between binge drinking and late life cognition. These studies found binge drinking at midlife to be associated with increased risk of cognitive impairment (203) and dementia (204) but both were based on a relatively small cohort of Finnish twins. In the present study this finding could not be replicated with cognitive test scores in a much larger sample. Interestingly, a prospective study in Novosibirsk found a higher risk of cardiovascular death in regular heavy drinkers but no association with episodic binge drinking (71), and preliminary analyses suggest no effect of binge drinking on total and cardiovascular mortality in this cohort (unpublished). The lack of an association between binge drinking and cognition is, therefore, consistent with the lack of adverse effects of binge drinking on cardiovascular disease in this cohort.

In this study, type of alcohol was not consistently associated with cognitive performance. Recent reviews (186,232) suggested that wine drinking may be associated with better cognition than drinking beer or spirits, but this finding was based on a relatively small number of studies. It has been suggested that polyphenolic antioxidants, especially resveratrol, contained in wine may be primarily responsible for cardioprotective effects associated with moderate alcohol consumption and may also have positive effects on the brain. Some studies have suggested that wine may reduce vascular risk to a greater extent than beer (217) or spirits (218), but other studies found no difference in cardiovascular risk reduction by alcohol type (219,220).

There is also considerable overlap between the mechanisms hypothesized to underlie the association between alcohol and cardiovascular disease, and resveratrol and cardiovascular disease, so it has been suggested that differences between wine and alcohol in relation to their effects on cardiovascular health may have been overstated (216). On the other hand, studies have shown preference for wine to be positively associated with more advantaged socioeconomic position (233,313–315), higher initial cognitive ability (233,316) and healthier lifestyles (314,317). For example, in the 1936 Scottish birth cohort, childhood cognitive ability and adult social class were positively associated with preference for wine (233) and, after adjusting for both factors, positive associations were observed in men between wine and verbal ability and spirits and memory, and negative associations between beer and verbal ability. In women, alcohol intake, primarily derived from wine, was associated with better verbal ability and memory. However, the reported associations were modest.

Although a positive relationship between wine preference and socioeconomic position has been found in several populations, this association may not be universal. For example, one study found wine consumption to be positively associated whereas consumption of beer and spirits negatively associated with education and socioeconomic position in Northern Ireland but not in France (313). In this thesis, preference for wine was generally significantly and positively associated with education across centres and genders, while there was greater variability across centres and genders in the strength and direction of association between education and preference for spirits and beer.

In conclusion, in these Central and Eastern European populations alcohol consumption was only modestly associated with cognitive function in middle-aged and older persons, except for the markedly lower scores in Czech and Polish abstainers and Russian former drinkers with poor health. Better cognitive performance was observed at moderate intakes in men and higher drinking frequencies in women. In addition, the present study suggests that, at least in men, alcohol intake above moderate levels may be associated with slightly worse cognitive performance. Slightly worse cognitive scores were also observed in women consuming high quantities of alcohol in a single drinking occasion. Binge drinking and alcohol type were not consistently associated with cognitive function. This suggests that in these populations binge drinking may not have an effect on cognitive function after accounting for total alcohol intake, although the finding requires confirmation in other settings. In addition, the findings also do not unequivocally support the view that wine drinking is associated with better cognition relative to drinking spirits or beer. The evidence on cognitive risks and/or potential benefits of different levels and patterns of alcohol consumption and the underlying causal nature of the association between alcohol and cognitive function remains insufficient to warrant specific recommendations about safe drinking levels or patterns.

5.5. Smoking and cognitive function

The previous section considered the results on alcohol consumption and mid to late life cognitive function. This section discusses the results of analyses on the other core health behaviour, smoking, presented in Chapter 4, Section 4.4. High rates of smoking and smoking-related mortality, particularly from cardiovascular disease, have been observed among men in Central and Eastern Europe (66). Moreover, during the transition smoking rates increased significantly in women (73). The public health implications of smoking are enormous in Central and Eastern Europe, especially in FSU countries, and smoking is also likely to have important consequences for the health of the region's older population.

In this study in four Central and Eastern European population samples cigarette smoking was associated with poorer mental speed performance. In contrast, smoking was not associated with memory, verbal fluency and global cognition. In women, quitting smoking was associated with better cognitive performance, compared to lifelong non-smoking. Pack years of smoking, a measure of lifelong exposure to cigarettes, was not significantly associated with cognitive performance, except for a weak association between the number of pack years and mental speed in men, which became insignificant after adjustment for health-related factors.

In addition to the general limitations of this thesis, the results of this study should be interpreted in the light of some specific considerations. First, smoking measures were based on self-reports. Data on smoking and cognitive function were collected at a single time point, and smoking history was assessed retrospectively. Self-reported data are subject to reporting

bias and, in the case of smoking history, recall bias. Although agreement between self-reported and serum cotinine-based measures of smoking is relatively high, there is a tendency for smoking prevalence to be underestimated based on self-reports (318). If the probability of underreporting increased with poor cognition, this would be expected to bias the association towards the null (245). However, at an average age of 60 years this is still a relatively young sample and significant reporting bias due to cognitive impairment seems unlikely. In calculating pack years it is assumed that the number of cigarettes smoked was constant for the duration of smoking. However, smoking patterns may change over time. In addition, both the number of cigarettes smoked per day and age at starting (and quitting) smoking may have been reported imprecisely.

Current smoking status is generally reported with relatively high accuracy (318,319). In comparison, retrospective reports about smoking may be less reliable than contemporaneous reports and self-reported measures of the number of cigarettes smoked tend to substantially underestimate actual consumption (320). It is also possible that heavy smokers systematically underreport the number of cigarettes typically smoked. These factors may result in misclassification error and under the simple model would be expected to bias the associations towards the null. In this study, smoking measures referred to cigarette smoking and did not specifically ask about other forms of tobacco. However, cigarette smoking is by far the most common.

Second, previous research has shown that selective non-participation and attrition, resulting in part from higher premature mortality among smokers, may lead to an underestimation of the associations between smoking and cognition and this is already apparent in middle age (321). In this study smokers were found to be less likely to participate based on a survey

conducted in non-responders (251) and were also disproportionately less likely to attend the re-examination clinic in Czech towns, Novosibirsk and Krakow. Thus, the associations between smoking and cognitive function presented here are probably an underestimate. However, sensitivity analyses (shown in Appendix XIII, pg. 269) comparing participants who had baseline cognitive data but were lost to follow-up with those who remained in the study, suggested that attrition is unlikely to alter the pattern of results.

Despite its limitations, this is the first study of smoking and cognitive function in middle-aged and older persons in Central and Eastern Europe. Smoking is an important contributing factor to the high mortality in Eastern Europe (322) and may also be expected to play a role in health of the region's older population. Among the strengths of this study are a large population-based sample and high statistical power of the pooled analysis, utilizing data from several neuropsychological tests assessing multiple aspects of fluid cognition and measures of smoking history in addition to current smoking status.

Previous studies have reported associations between smoking status and baseline cognitive performance in several domains, including global cognition, mental speed (245,247) and cognitive flexibility (241,323), and greater declines among smokers in memory (241,243,247), cognitive flexibility (241) and global cognition (241–243). A study in a sample of independently living men found smoking to be one of the strongest predictors of reduced processing speed and a lower MMSE score (324). Some studies, however, reported insignificant or inconsistent associations (248,325,326). The results presented here are similar to those reported by Richards et al. (247) and Nooyens et al. (241) (the former adjusting for childhood cognition), where smoking status was found to be associated with baseline mental

speed but not baseline memory; however, in these studies smoking was associated with a decline in memory but not in mental speed.

In this study, the number of pack years was not associated with cognitive function. Significant associations of cognitive performance with smoking status but no dose-response association with pack years have been reported in several studies (245,248,305,321,327), and Richards et al. (247) observed poorer mental speed performance only in heavy smokers. As already mentioned, pack years are likely to be measured less accurately than current smoking status and the resulting misclassification could bias the associations towards the null. In this study, an association between pack years and letter search was detected in men but was lost in pooled analysis after controlling for health measures.

It has been also suggested that the absence of a dose-response association with pack years may be a consequence of selective non-participation and attrition among heavy smokers (321). Alternatively, one study suggested that the inconsistency between significant associations of cognitive function with smoking status but no dose-response association could arise from selection by higher initial cognitive ability among lifelong non-smokers, and particularly, those who quit smoking (248). However, other studies observed an association between increasing number of pack years and faster cognitive decline (241–243) or reduced baseline cognitive scores (323). In a study of 1936 Scottish birth cohort processing speed and general cognitive ability at age 70 were associated with current smoking but and not with pack years, after adjusting for socioeconomic position and childhood cognitive ability (245). In this study, the effect of pack years but not current smoking status on cognitive function in old age was completely explained after adjusting for childhood cognitive ability. The authors concluded that continuing smoking in old age may be particularly harmful for cognitive

health. Similarly, in the study by Richards et al. (247) smoking was also associated with mental speed performance, after adjusting for childhood cognitive ability.

In this study, smoking status was significantly associated with reduced mental speed in both genders. However, in men there was significant heterogeneity among centres in the associations of mental speed with smoking status and pack years, with significant results observed only in Novosibirsk and Kaunas. In several previous studies the effects of smoking on processing speed were particularly marked (245,247,324). It could be that mental speed is especially sensitive to the effects of continuing smoking in middle and older age. Letter search tasks are particularly sensitive to age-associated decline (328) and may also be particularly sensitive to physiological functioning.

It is not entirely clear why this study did not detect associations between smoking and other measures of cognition. In other studies negative associations with smoking have often been observed for several cognitive measures and/or global cognition in middle-aged and older adults (241,242,321,324). In addition, in most studies exposure to cigarette smoke was associated with increased risk of preclinical outcomes (249), Alzheimer's disease (244) and dementia (249). Other than the possibility that smoking status partly reflects selection by initial cognitive function or other potential confounders (245), many constituents of tobacco smoke have known toxic effects on the brain, cardiovascular and pulmonary systems (249).

Potential mechanisms for the harmful effects of smoking include increased oxidative stress in the brain and other organs, increased inflammatory response, which may promote atherosclerosis and AD-related neuropathology, and increased cardiovascular risk (249). One study found a negative association between smoking and measures of microstructural

integrity of cerebral white matter, which appeared to mediate the associations between smoking status and poorer performance on cognitive tests (329). This study also found that measures of white matter integrity did not differ significantly between never smokers and former smokers who stopped smoking more than 20 years earlier. The observed effects of smoking on cognitive function could also (partly) result from indirect effects from conditions other than cardiovascular disease. Another potential mediator is lung function (249). Notably, lung function, measured by forced expiratory volume after 1 second, was found to be negatively associated with cognitive function, independently of smoking (245,330,331).

In this study, the association between smoking status and mental speed was largely unaffected by adjustment for self-reported history of cardiovascular disease, stroke and high blood pressure or further adjustments for vascular measures from the baseline clinical examination, including BMI, systolic and diastolic blood pressure, resting pulse, and high- and low-density lipoproteins, in additional analyses. To the extent that these measures adequately capture cardiovascular risk, it does not appear to explain this association.

Smoking rates estimated in this study are consistent with other studies in the region. High smoking rates among men are well documented in Central and Eastern Europe, particularly in Russia (73,274,332). Male smoking rates are also higher than in Western Europe (332). However, for women the converse is true. Given the low rates and cultural unacceptability of smoking among women of this age group, it is possible that women were more likely to underreport smoking than men (333). This would lead to an underestimation of the associations in women relative to men. However, effect sizes for smoking and mental speed, at least, were similar in both genders. In these cohorts the extent of social patterning of smoking was much greater in men than in women. Unlike in women, large educational

differentials in smoking rates were observed in men. This finding is consistent with earlier studies in Central and Eastern Europe which also found greater socioeconomic differences in smoking among men (275,276).

In women, former smokers had better cognitive test scores than never smokers. Possible explanations include selection by higher initial cognitive ability among those who quit smoking or improvement in other health-related behaviours in former smokers (321). Cessation of smoking was shown to be positively associated with childhood cognitive ability in several studies (245,334,335). In contrast, not all of these studies found childhood cognitive ability to also predict (inversely) the uptake of smoking (335), which was attributed to social attitudes to tobacco over a particular historical period (245). It is conceivable that similar contextual mechanisms may have operated in Central Europe, and particularly the FSU, in these cohorts. Rates of ever smoking in men are very high and thus childhood cognitive ability may not have been as strong an influence on the uptake of smoking in men. On the other hand, in women the association could have plausibly been in the opposite direction; smoking rates in women in these cohorts are low, and in Novosibirsk and Kaunas smoking is positively associated with education in women.

In a study of British civil servants quitting smoking was associated with improvement in other health-related behaviours, including alcohol intake and dietary choice, and this was responsible for better cognitive performance among former smokers (321). In this study results for female former smokers were little affected by adjustments for current alcohol intake and self-reported medical history or adjustments for leisure-time physical activity in additional analyses. However, assessment of health behaviours was incomplete and residual confounding remains a possibility. For example, dietary choice was not among the health

behaviours included in this study. Smoking is associated with unhealthy patterns of nutrient intakes (336), while healthy dietary choice has been linked to better cognitive outcomes in older age (337).

Overall, there was limited evidence to suggest that alcohol consumption systematically modifies the relationship between smoking and cognitive function in these populations, at least cross-sectionally. There was some evidence to suggest that the association between smoking and letter search speed varies with the level of alcohol intake in men and drinking frequency in women. Additionally, in women the interaction between smoking and drinking frequency was also borderline statistically significant for delayed recall and global cognition. The results in men were mostly explained by better mental speed scores in former smokers at higher levels of alcohol consumption. In women, current smokers who drank frequently had worse letter search, delayed recall and global cognitive scores than never smokers who drank occasionally (reference group).

A previous longitudinal study in British civil servants reported lower baseline cognitive scores in moderate drinkers who were current smokers compared to moderate drinkers who were never smokers, against the trend of increasing baseline cognitive scores with increasing alcohol consumption (250). This study also found weak evidence of faster decline on a measure of global cognition in heavy smokers who were also heavy drinkers compared to non-smoking moderate alcohol drinkers. In these Central and Eastern European populations, lower baseline cognitive scores were observed for some tests of cognition in current smokers who drank frequently, compared to never smokers who drank occasionally, but only in women.

In conclusion, smoking was associated with reduced mental speed performance but not with other tests of cognition. Former smokers did not have lower cognitive scores compared to never smokers and female former smokers actually had better cognitive function. Smoking history, measured by pack years, was generally not associated with cognitive performance. Despite the relatively weak association between smoking and cognitive function, these results should not discourage stop-smoking interventions targeting middle-aged and older smokers in Central and Eastern Europe considering that other health behaviours are also more likely to be poor in smokers, the well-known health benefits of quitting and the possibility of an independent association between smoking and cognitive decline.

5.6. Meaning and implications of the findings

While the previous sections in this chapter provided specific discussions of the results from analyses of cognitive function with life course SEP, alcohol consumption and smoking as exposures of interest, this section attempts to situate the findings within a broader context and follows on with a discussion of the overall meaning and wider implications of the key findings of this thesis as well as potential policy implications and concluding comments.

The pathways through which SEP measures from across the life course affect cognitive function in middle and older age are still not well understood. Emerging evidence of broadly similar patterns of associations between life course SEP and mid to late life cognitive function found across different settings, including the four Central and Eastern European populations in this study, and settings as diverse as the USA (122), Great Britain (126), China

(175), and Scandinavia (123,127) suggests that, as with many other health outcomes, the mechanisms involved may be pervasive. In addition, the findings also suggest that, as with some other aspects of life under socialism, such as, for example, access to education (100), the fundamentally different economic structure of the communist system, in the several decades of its existence, did not necessarily result in a significantly different pattern of inequalities in health outcomes from contemporary capitalist societies.

In this thesis, mother's education (and, to a lesser extent, also father's education) was directly associated with mid to late life cognitive function in several centres (Kaunas exempt). Compared to paternal measures, mother's education may better reflect familial factors which are associated with cognitive development such as parenting practices (115), parental aspirations and encouragement, cognitive stimulation and environmental enrichment in the home, childhood nutrition and other behaviours, such as breastfeeding, which may impact on child development (338).

In addition, maternal education may also plausibly be associated with prenatal and postnatal growth and birth weight, an indicator of prenatal growth, appears to be associated with childhood cognitive development (339). However, while a recent study identified prenatal and postnatal growth as potential risk factors for poorer lifetime cognitive ability and cognitive decline (114), earlier studies generally failed to find long-term associations between birth weight and cognitive function after accounting for cognitive development (340,341). Finally, while several mechanisms have been proposed to account particularly for the association between mother's education and cognitive function, one mechanism which is likely to contribute to associations of both maternal and paternal education with mid to late

life cognitive function is parental intelligence, since cognitive ability is a highly heritable trait (342,343).

One possible explanation for the direct association between childhood SEP measures and mid-late life cognition is that it is a result of a latent process or some form of biological programming, such that early life exposures produce long-lasting changes in the structure or function of physiologic systems or processes, for example, inflammation and endocrine or stress response dysregulation, the effects of which on cognitive function only become fully apparent or become exacerbated with cognitive ageing. This is consistent with the "latency" or critical period model of the life course and, indeed, this was the preferred interpretation in some cross-sectional studies with retrospective measures of childhood SEP, reporting direct associations between childhood factors and cognitive function in midlife or old age (121,123,172).

However, two prospective birth cohort studies, which, among other things, also controlled for childhood cognitive ability, did not find significant direct effects of childhood SEP on adult or late life cognition (128,174). Only one cohort study in Danish conscripts found a modest direct effect of father's occupation on midlife cognition, after accounting for adolescent cognitive ability, education attained by age 18 and adult SEP (344). Thus, an alternative possibility is that the direct associations observed in some studies are, in fact, residual effects, resulting from incomplete adjustment for hypothesized mediators, which include childhood cognitive development, education and adult SEP. Consistent with some earlier studies (120,121), in this thesis the direct path from parental education to cognition was generally modest and not entirely consistent across centres and genders. Since in this study it was not possible to adjust for childhood cognitive development and adult occupation, residual effects

of childhood SEP on cognition cannot be ruled out. Notably, in these cohorts mother's (and father's) education was a significant predictor of participants' attained education, which, in turn, was the main mechanism indirectly linking childhood SEP measures with mid to late life cognitive function. Since childhood socioeconomic disadvantage also tends to be associated with poor cognitive development, which is, in turn, associated with lower subsequent socioeconomic attainment, this further adds to the tracking of socioeconomic disadvantage and thus poor cognitive function across the life course.

In this study, childhood material conditions showed a significant direct association with cognition only in Russian women, possibly because these Russian cohorts experienced much greater material hardship. To the extent that the basic amenities index adequately captures childhood material circumstances, this suggests that factors associated with other aspects of socioeconomic environment in childhood may be more important for cognitive function in later life than material conditions, unless early material disadvantage is severe. Although latent long-term effects of material conditions on cognition are plausible, the possibility of residual effects due to incomplete adjustment for relevant mediators may also apply in this case. For example, in the 1946 British birth cohort the long-term effects of early life material adversity on adult cognition were largely accounted for by the effects of adversity on childhood or adolescent cognitive ability or by differences in educational attainment and adult socioeconomic position, with the exception of a small direct effect of poor material home conditions on mental speed at age 53 (129).

In line with previous research (15,122,123,126,131), in this thesis education was consistently and strongly associated with cognitive function but the magnitude of the association varied across centres. The results were not entirely expected and contextual factors which could

plausibly account for some of these differences were previously outlined in Section 5.3. The magnitude of the education-cognition association was similar in Czech towns and Krakow, strongest in Kaunas and weakest in Novosibirsk. The similarities between Czech towns and Krakow are not particularly surprising, given their shared Central European history. The results for Novosibirsk and Kaunas are less clear. During the Soviet period, Russia and Lithuania were relatively comparable in terms of socioeconomic development, living standards and health indicators and both countries experienced a relatively sharp increase in income inequality in the early phases of transition. However, the countries have since diverged in these indicators and increasingly so (345). Also, pre-WWII Lithuania had a capitalist economic system and Western-influenced culture. Potential explanations for the education-cognition link are several and include ability-based selection into education, which has been hypothesized to increase in importance with decreasing importance of parental background (293,346), provision of mental stimulation and enriched environments by education with potentially lasting benefits for cognitive reserve since education appears to benefit cognition independently of initial level of cognitive ability (144,145), and positive associations of education with occupation, material well-being, healthier lifestyles and better general health.

Current household asset ownership was significantly associated with cognitive function in men in all centres, while this path was generally somewhat less important in women. One of the hypothesized pathways linking adult SEP to mid and late life cognition is through adult occupation, which defines the cognitive complexity of work environment (149). Another hypothesized pathway is through occupational exposures which result in poorer health or direct exposure to work-related neurotoxins (111). For example, occupational exposure to lead has been linked to faster cognitive decline (347). A measure of lifelong occupation was

not available in these cohorts. The correlation between occupation and material circumstances, especially income from wages, is thought to have been relatively weak under socialism in Central and Eastern Europe as a result of wage levelling policies. It is not clear how well measures of current material circumstances correlate with lifelong occupation in these cohorts and such indices may not differentiate well among pensioners. Contrastingly, correlation between education and occupation is believed to have been quite strong under socialism, at least anecdotally. Therefore, in these cohorts education could plausibly act as a surrogate for occupation to a greater extent than current material circumstances.

Material inequalities were certainly present during communism. Ownership of durable assets has been shown to differentiate between different socio-occupational groups in a cross-section in these countries; households of white-collar workers were best equipped with durable goods, followed by households of manual workers, pensioners and, lastly, farmers (348). Retirement has been suggested to increase the risk of cognitive decline but evidence is inconclusive (349). In addition, longer time spent in active employment and postponement of retirement has been suggested to be more common among individuals in higher-level occupations and/or with higher initial cognitive ability (42). In this study pensioners without employment were more likely to own fewer durable assets and generally also had worse cognitive performance than working participants or working pensioners but controlling for a measure of current economic activity in additional regression analyses did not affect the association between cognitive function and asset ownership (or other SEP measures).

Other plausible pathways linking adult SEP to cognitive function in middle and older age include access to health care, socioeconomic differences in physical illnesses such as cardiovascular disease, diabetes and other conditions which are associated with cognitive

decline and stress associated with absolute and/or relative deprivation. These pathways might have become more important in recent decades as income and health inequalities have increased significantly in all former socialist countries (85) but especially in those countries with the greatest increases in inequalities.

A further and related pathway which may link adult SEP to middle and older age cognitive function is through health behaviours (111), including alcohol consumption and smoking. In this study, alcohol consumption and smoking were socially patterned, particularly among men. Social patterning was stronger with regard to education than current material circumstances. However, associations between cognitive function and these two core health behaviours were relatively weak. There was some evidence of worse cognitive performance in heavy drinkers and among smokers lower cognitive scores were found for the test of mental speed. In addition, better cognitive function was observed with increasing drinking frequencies in women, at moderate drinking levels in men and in female former smokers. However, this is likely to be a result of selection among moderate drinkers and former smokers. In the case of moderate drinking, this is reinforced by the null findings from a recent Mendelian randomization study (350) in Chinese moderate male drinkers, for whom a previous observational study (239) found a protective cognitive effect of moderate alcohol consumption.

Consequently, the role of the two main health behaviours, alcohol consumption and smoking, in mediating the associations, at least cross-sectional, between SEP and mid to late life cognition in these cohorts is likely to be relatively minor. In regression analyses associations of SEP measures from across the life course with cognitive function were largely unaffected by adjustments for alcohol intake and smoking status and subsequently these measures were

not used in structural equation analysis. This might not have been expected on the basis of significant contributions of high alcohol consumption and smoking to higher mortality in Eastern Europe (20,65,322) and notable socioeconomic differentials in mortality in the region (65). In another study in this cohort alcohol consumption and smoking were also not important mediators between current socioeconomic factors and functional limitations, owing perhaps to the relatively weak associations between these two health behaviours and functional limitations (probability of functional limitations was raised only among abstainers from drinking and male smokers) (83). Cognitive functioning has been shown to predict mortality (6,351), and this association may be partly explained by health (351) and health behaviours (352). A degree of overlap might also be expected between risk factors for poorer cognitive function and mortality in these populations, considering, for example, the contribution by cardiovascular disease to high mortality in the region and their associations with cognitive health. However, as with functional health (83), the role of alcohol and smoking in mediating this relationship is unlikely to be particularly strong, at least as far as the findings presented in this thesis are concerned.

The findings of this thesis may not only have implications for public health but also wider social significance. First, the findings on life course SEP suggest that in the long-term interventions to reduce social inequalities throughout the life course may impact cognitive health in later life. However, interventions starting in childhood may be most effective given the apparent importance of social trajectories and attained education for cognitive outcomes in mid and later life. This is particularly noteworthy considering that social inequalities have increased dramatically throughout much of Central and Eastern Europe since 1990 together with poverty levels, particularly among children (85).

Second, in the short-term interventions to improve cognitive functioning of middle-aged and older persons in Central and Eastern Europe may be preferentially targeted at the more disadvantaged socioeconomic groups, identified by low education. These groups also include a disproportionate number of heavy drinkers and smokers, especially among men. Although in these populations cross-sectional associations between both alcohol consumption and smoking and cognitive function were generally modest, there was some evidence to suggest that smoking and, in men, heavy drinking may independently contribute to reduced performance in some aspects of fluid cognition in middle and older age.

5.7. Future research

With continued population ageing, effective treatment for dementia remaining elusive and research on cognitive ageing, and healthy ageing in general, still in the early stages in Central and Eastern Europe, potential avenues for future research are many. This section recommends, based on the findings of this thesis, what might constitute future research priorities.

Future research should focus on associations between SEP, alcohol consumption and smoking with cognitive decline in longitudinal data, as they become available for this and other studies based on Central and Eastern European populations. Factors associated with baseline cognitive performance are not necessarily also associated with the rate of cognitive decline (16,71,136). The pathways which plausibly link SEP from across the life course with cognitive function in middle age and later life remain poorly understood. The contribution to

cognition of other health behaviours, such as dietary pattern and physical activity, has not yet been studied in these populations and few studies have examined the combined effects of multiple health behaviours on cognitive health (337).

Future research on cognitive ageing could also make a significant contribution through more explicit and careful modelling of the possible implications of missing data and longitudinal attrition, particularly by modelling the potential consequences of plausible missing not at random (MNAR) scenarios and by generating relevant contextual knowledge to inform these endeavours. A recent first step in this direction is Salthouse's analysis (353) of selective attrition in a longitudinal study of cognitive ageing, which indicated that selective attrition is a complex phenomenon but may not necessarily lead to biased estimates of longitudinal change under the assumption of missing at random. In addition, modelling of missing data in cognitive ageing research may benefit from greater use of causal modelling approaches (354). For example, directed acyclic graphs (DAGs), used for representing causal relations between variables, can also be very informative for representing the hypothesized missingness mechanisms and deciding whether or not parameter estimates are likely to be biased as a result of missing data.

Future population studies should be designed to also include measures of cognitive impairment and dementia. Direct population-based estimates for the prevalence of cognitive impairment and dementia in Central and Eastern Europe, especially Russia, are even sparser (355) than studies with neuropsychological test measures. Consequently, studies on risk and protective factors for mild cognitive impairment and dementia in these populations are also lacking.

The role of cardiovascular factors in mediating the associations between core health behaviours, alcohol consumption and smoking, and cognitive ageing requires further research. Cardiovascular risk is one of the main mechanisms hypothesized to mediate the associations between alcohol consumption, smoking and other health behaviours with cognitive ageing but relatively few studies have attempted to comprehensively test this hypothesis. Recent evidence suggests that the apparent protective effect of moderate alcohol consumption on cognition may be the result of selection among moderate drinkers (234,350) rather than better cardiovascular health but this has yet to be established for heavier drinkers. Interestingly, in this study binge drinking was not independently associated with cognitive performance and one possible explanation for this is the apparent lack of associations between binge drinking and cardiovascular disease in these populations (71), and emerging evidence on the lack of associations between binge drinking and markers of cardiovascular disease risk in this study (356). These findings require replication with longitudinal data.

This thesis uncovered significant variation among centres in the strength of associations between life course SEP and mid to late life cognitive function. Additionally, intraregional differences in cognitive ageing and associated risk factors in Central and Eastern European populations may be systematically explored and exploited. An earlier study in this cohort found significant intraregional differences in the rate of cognitive ageing in a cross-section, which were only partly explained by conventional risk factors (81). Such studies, particularly if longitudinal, may help to elucidate the determinants of cognitive ageing.

Finally, comparisons of Central and Eastern European populations with other ageing cohorts will likely represent an area of growing importance, facilitated also by the fact that ageing-related outcomes available in this study are comparable with many other studies of ageing,

including the English Longitudinal Study of Ageing and the Survey of Health, Ageing and Retirement in Europe.

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Appendix I. Instruments for measuring cognitive function

1. Word learning task: Word list included the following 10 nouns: Water, Church, Doctor, Palace, Fire, Garden, Sea, Village, Baby, and Table. Words played on tape, recalled three times within one minute and once after a delay.

2. Verbal fluency: The task was introduced in the following way: "Now, I would like you to name as many different animals as you can think of. You have one minute to do this. I will tell you when to stop. Is this clear?" Repetitions or redundancies (e.g. black cow, brown cow etc.) were not counted. However, breeds and gender or gender-specific names (e.g. bull, cow, steer, heifer, calf) each received credit.

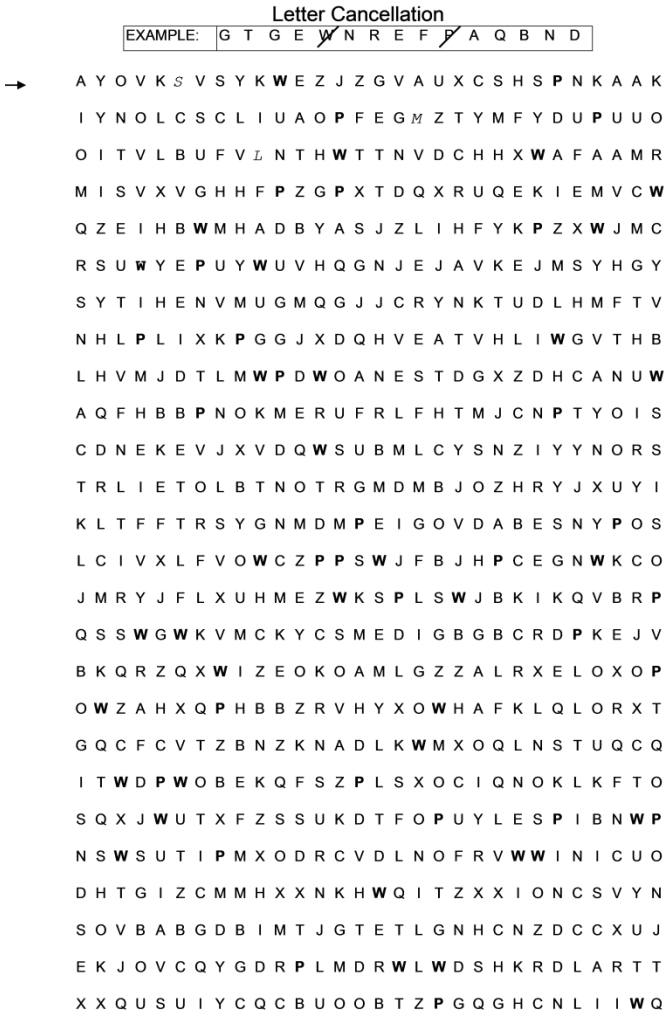

Figure I-1 Letter search task

3. Letter search (aka letter cancellation, visual search, mental speed and concentration test): The original instrument, an illustration of which can be seen on the left-hand side, was presented on an A4 paper sheet. Participants were instructed to cross out P and W (Ш in Russia) as quickly and accurately as possible within 1 minute. Where cognitive assessment was conducted in a clinic, prior to the examination participants were asked to bring glasses and hearing aids to the clinic.

Appendix II. Instruments for measuring alcohol intake

Figure I-1 shows the graduated frequency (GF) questionnaire used in Czech towns, Novosibirsk and Krakow at the 2002-2005 baseline questionnaire with accompanying instructions; shortened versions of the baseline questionnaire were used at re-examination in 2006-08 and Kaunas baseline. Additional questions on typical weekly alcohol intake of wine, beer and spirits, included at baseline in all centres and repeated at follow-up, can be found below the GFQ.

1.) The graduated frequency (GF) questionnaire

When responding to the GF questionnaire, participants were given the following instructions: **“**The next few questions are about how much wine, beer and spirits you may have had during the last 12 months. When we say one drink, we mean 0.5 litre of beer, 2 dl glass of wine, or 5 cl of spirits. Please answer each question below – i.e. cross out a square in each row - to indicate how often you had that amount of alcohol during one day. Here is an example how to calculate correct amount of alcohol on a single occasion: if you had 0.7 l bottle of wine AND two 5cl measures of spirit in a single occasion you had 3.5 drinks of wine and 2 drinks of spirit which is a total of 5.5 drinks. Then you need to choose correct column to indicate how often in the last year you had such amount of alcohol. ”

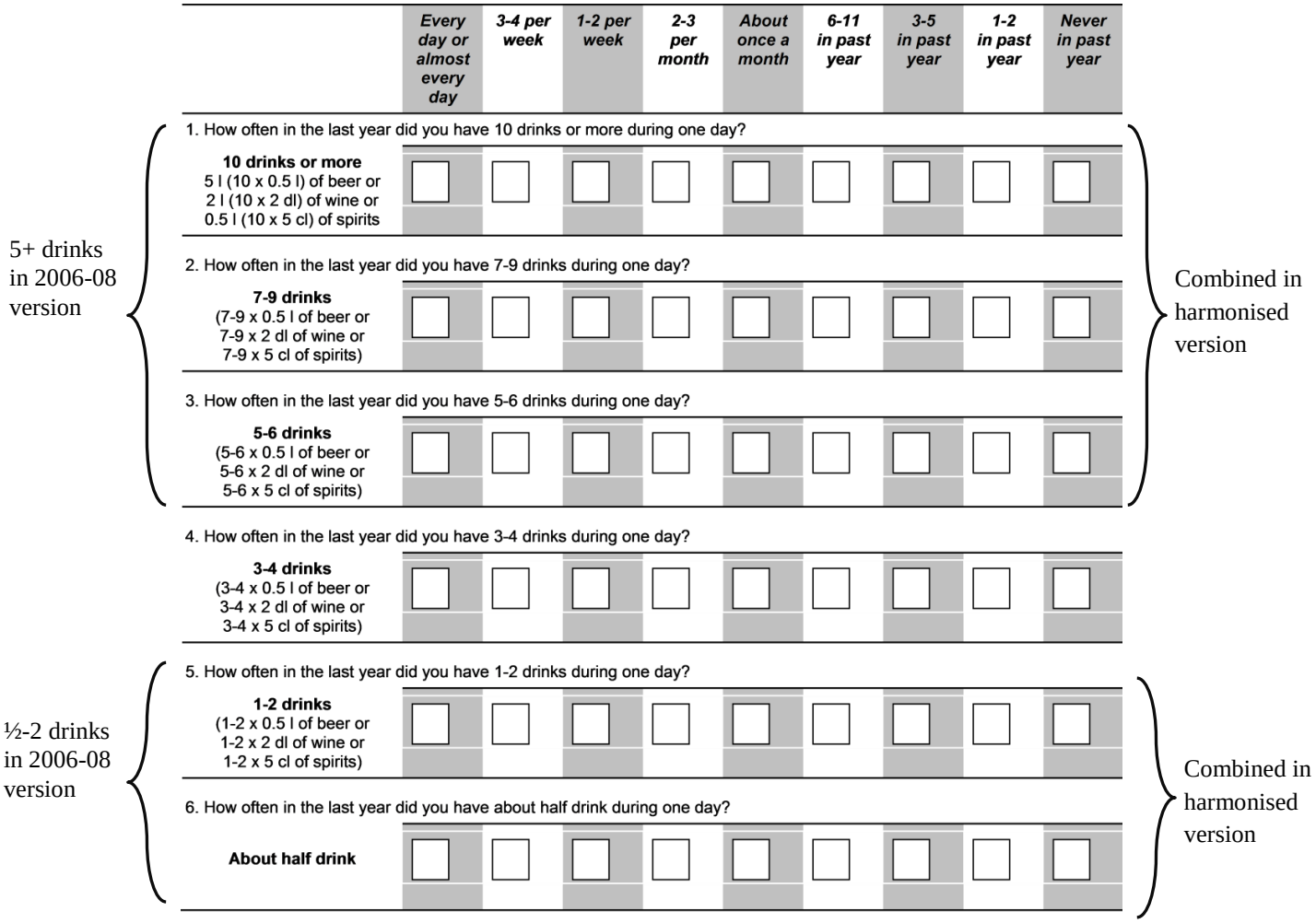

Figure II-1 Graduate Frequency Questionnaire used at 2002-2005 baseline

2.) Additional questions on typical intake by type of alcohol

1. How much beer (litres) do you usually drink during one week?
2. How much wine (decilitres) do you usually drink during one week?
3. How much spirits (decilitres) do you usually drink during one week?

Appendix III. Regression analyses of life course SEP and cognition

This section includes results from preliminary regression analyses of SEP and cognitive function for various levels of adjustment for men and women.

Table III-1 Results for age-adjusted regression models of SEP measures and cognitive function in men

	Word recall		Verbal fluency		Letter search		Delayed recall		Global cognition	
	b	SE	b	SE	b	SE	b	SE	b	SE
Czech towns (n=2,048)										
Mother's education										
Less than primary	0.00		0.00		0.00		0.00		0.00	
Primary	0.34*	(0.15)	0.25	(0.16)	0.13	(0.16)	0.14	(0.15)	0.22*	(0.11)
Secondary	0.61***	(0.15)	0.51**	(0.16)	0.32*	(0.16)	0.40**	(0.15)	0.46***	(0.11)
University	0.68**	(0.22)	0.78***	(0.23)	0.50*	(0.23)	0.37	(0.22)	0.58***	(0.16)
Childhood amenities	0.05**	(0.02)	0.05**	(0.02)	0.05**	(0.02)	0.04*	(0.02)	0.05***	(0.01)
Education										
Primary	0.00		0.00		0.00		0.00		0.00	
Secondary	0.65***	(0.11)	0.49***	(0.11)	0.59***	(0.11)	0.41***	(0.11)	0.54***	(0.08)
University	1.15***	(0.11)	0.91***	(0.12)	0.94***	(0.12)	0.81***	(0.12)	0.95***	(0.08)
Household assets	0.08***	(0.01)	0.08***	(0.01)	0.06***	(0.01)	0.06***	(0.01)	0.07***	(0.01)
Novosibirsk (n=2,655)										
Mother's education										
Less than primary	0.00		0.00		0.00		0.00		0.00	
Primary	0.11*	(0.05)	0.11*	(0.05)	0.25***	(0.05)	0.16**	(0.05)	0.16***	(0.04)
Secondary	0.25***	(0.05)	0.21***	(0.05)	0.23***	(0.05)	0.25***	(0.05)	0.23***	(0.04)
University	0.46***	(0.08)	0.45***	(0.08)	0.48***	(0.09)	0.39***	(0.08)	0.44***	(0.06)
Childhood amenities	0.05***	(0.01)	0.00	(0.01)	0.02	(0.01)	0.03**	(0.01)	0.03**	(0.01)
Education										
Primary	0.00		0.00		0.00		0.00		0.00	
Secondary	0.26***	(0.06)	0.14*	(0.06)	0.32***	(0.06)	0.32***	(0.06)	0.26***	(0.04)
University	0.60***	(0.06)	0.53***	(0.06)	0.75***	(0.06)	0.58***	(0.06)	0.61***	(0.04)
Household assets	0.08***	(0.01)	0.11***	(0.01)	0.10***	(0.01)	0.07***	(0.01)	0.09***	(0.01)
Krakow (n=3,567)										
Mother's education										
Less than primary	0.00		0.00		0.00		0.00		0.00	
Primary	0.23***	(0.05)	0.17***	(0.05)	0.31***	(0.05)	0.17**	(0.05)	0.22***	(0.04)
Secondary	0.50***	(0.05)	0.46***	(0.06)	0.53***	(0.06)	0.34***	(0.06)	0.46***	(0.04)
University	0.69***	(0.09)	0.67***	(0.09)	0.88***	(0.10)	0.47***	(0.09)	0.68***	(0.07)
Childhood amenities	0.07***	(0.01)	0.08***	(0.01)	0.08***	(0.01)	0.06***	(0.01)	0.07***	(0.01)
Education										
Primary	0.00		0.00		0.00		0.00		0.00	
Secondary	0.40***	(0.05)	0.36***	(0.05)	0.32***	(0.06)	0.29***	(0.06)	0.34***	(0.04)
University	0.92***	(0.05)	0.84***	(0.06)	0.75***	(0.06)	0.65***	(0.06)	0.79***	(0.04)
Household assets	0.10***	(0.01)	0.10***	(0.01)	0.11***	(0.01)	0.09***	(0.01)	0.10***	(0.01)
Kaunas (n=2,790)										
Mother's education										
Less than primary	0.00		0.00		0.00		0.00		0.00	
Primary	0.22***	(0.05)	0.06	(0.05)	0.28***	(0.05)	0.14**	(0.05)	0.18***	(0.04)
Secondary	0.43***	(0.06)	0.21***	(0.06)	0.52***	(0.06)	0.29***	(0.06)	0.36***	(0.04)
University	0.47***	(0.09)	0.40***	(0.09)	0.86***	(0.09)	0.30***	(0.09)	0.51***	(0.06)
Childhood amenities	0.03*	(0.02)	0.01	(0.02)	0.07***	(0.02)	0.02	(0.02)	0.03**	(0.01)
Education										
Primary	0.00		0.00		0.00		0.00		0.00	
Secondary	0.49***	(0.06)	0.30***	(0.06)	0.46***	(0.06)	0.43***	(0.06)	0.42***	(0.04)
University	0.91***	(0.06)	0.71***	(0.06)	0.98***	(0.06)	0.78***	(0.06)	0.84***	(0.04)
Household assets	0.09***	(0.01)	0.05***	(0.01)	0.09***	(0.01)	0.06***	(0.01)	0.07***	(0.01)

b=regression coefficient; SE=standard error

Adjusted for age and measurement wave only (SEP measures not mutually adjusted).

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table III-2 Results for age-adjusted regression models of SEP measures and cognitive function in women

	Word recall		Verbal fluency		Letter search		Delayed recall		Global cognition	
	b	SE	b	SE	b	SE	b	SE	b	SE
Czech towns (n=2,376)										
Mother's education										
Less than primary	0.00		0.00		0.00		0.00		0.00	
Primary	0.49***	(0.13)	0.29*	(0.13)	0.35**	(0.13)	0.48***	(0.13)	0.40***	(0.09)
Secondary	0.78***	(0.13)	0.61***	(0.13)	0.50***	(0.13)	0.67***	(0.13)	0.64***	(0.09)
University	1.02***	(0.23)	1.02***	(0.23)	0.67**	(0.24)	0.99***	(0.23)	0.92***	(0.16)
Childhood amenities	0.06***	(0.02)	0.06***	(0.02)	0.05**	(0.02)	0.04*	(0.02)	0.05***	(0.01)
Education										
Primary	0.00		0.00		0.00		0.00		0.00	
Secondary	0.76***	(0.05)	0.65***	(0.05)	0.33***	(0.06)	0.52***	(0.06)	0.57***	(0.04)
University	1.11***	(0.07)	1.25***	(0.07)	0.57***	(0.08)	0.84***	(0.08)	0.94***	(0.05)
Household assets	0.08***	(0.01)	0.06***	(0.01)	0.05***	(0.01)	0.05***	(0.01)	0.06***	(0.01)
Novosibirsk (n=3,285)										
Mother's education										
Less than primary	0.00		0.00		0.00		0.00		0.00	
Primary	0.23***	(0.04)	0.21***	(0.04)	0.11*	(0.05)	0.23***	(0.04)	0.19***	(0.03)
Secondary	0.42***	(0.04)	0.40***	(0.04)	0.16***	(0.05)	0.38***	(0.04)	0.34***	(0.03)
University	0.54***	(0.07)	0.60***	(0.08)	0.23**	(0.08)	0.53***	(0.07)	0.48***	(0.06)
Childhood amenities	0.07***	(0.01)	0.03**	(0.01)	0.05***	(0.01)	0.05***	(0.01)	0.05***	(0.01)
Education										
Primary	0.00		0.00		0.00		0.00		0.00	
Secondary	0.40***	(0.05)	0.31***	(0.06)	0.37***	(0.06)	0.33***	(0.05)	0.35***	(0.04)
University	0.79***	(0.06)	0.75***	(0.06)	0.60***	(0.06)	0.65***	(0.06)	0.70***	(0.04)
Household assets	0.07***	(0.01)	0.09***	(0.01)	0.08***	(0.01)	0.07***	(0.01)	0.08***	(0.01)
Krakow (n=3,778)										
Mother's education										
Less than primary	0.00		0.00		0.00		0.00		0.00	
Primary	0.21***	(0.05)	0.30***	(0.05)	0.42***	(0.05)	0.18***	(0.05)	0.28***	(0.04)
Secondary	0.43***	(0.05)	0.61***	(0.05)	0.55***	(0.06)	0.31***	(0.06)	0.48***	(0.04)
University	0.67***	(0.08)	0.93***	(0.09)	0.75***	(0.09)	0.57***	(0.09)	0.73***	(0.07)
Childhood amenities	0.08***	(0.01)	0.09***	(0.01)	0.08***	(0.01)	0.06***	(0.01)	0.08***	(0.01)
Education										
Primary	0.00		0.00		0.00		0.00		0.00	
Secondary	0.46***	(0.04)	0.36***	(0.04)	0.43***	(0.05)	0.37***	(0.05)	0.41***	(0.03)
University	0.93***	(0.05)	0.89***	(0.05)	0.73***	(0.05)	0.76***	(0.05)	0.83***	(0.04)
Household assets	0.08***	(0.01)	0.06***	(0.01)	0.08***	(0.01)	0.06***	(0.01)	0.07***	(0.01)
Kaunas (n=3,389)										
Mother's education										
Less than primary	0.00		0.00		0.00		0.00		0.00	
Primary	0.27***	(0.04)	0.20***	(0.04)	0.17***	(0.04)	0.15***	(0.04)	0.19***	(0.03)
Secondary	0.43***	(0.05)	0.32***	(0.05)	0.37***	(0.05)	0.33***	(0.05)	0.36***	(0.04)
University	0.59***	(0.08)	0.67***	(0.09)	0.30***	(0.09)	0.35***	(0.09)	0.48***	(0.06)
Childhood amenities	0.04**	(0.01)	0.05***	(0.01)	0.05***	(0.01)	0.02	(0.01)	0.04***	(0.01)
Education										
Primary	0.00		0.00		0.00		0.00		0.00	
Secondary	0.63***	(0.05)	0.37***	(0.06)	0.56***	(0.06)	0.60***	(0.05)	0.54***	(0.04)
University	1.07***	(0.05)	0.88***	(0.06)	0.96***	(0.06)	0.95***	(0.06)	0.96***	(0.04)
Household assets	0.08***	(0.01)	0.05***	(0.01)	0.07***	(0.01)	0.06***	(0.01)	0.07***	(0.01)

b=regression coefficient; SE=standard error

Adjusted for age and measurement wave only (SEP measures not mutually adjusted).

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table III-3 Results for mutually-adjusted and health-behaviours adjusted regression models of life course SEP and cognitive function in men

	Word recall				Verbal fluency				Letter search				Delayed recall				Global cognition			
	Mutually adjusted		Health behaviours		Mutually adjusted		Health behaviours		Mutually adjusted		Health behaviours		Mutually adjusted		Health behaviours		Mutually adjusted		Health behaviours	
	b	SE	b	SE	b	SE	b	SE	b	SE	b	SE	b	SE	b	SE	b	SE	b	SE
Czech towns (n=2,048)																				
Mother's education																				
Less than primary	0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00	
Primary	0.26	(0.15)	0.23	(0.15)	0.18	(0.15)	0.15	(0.16)	0.08	(0.16)	0.05	(0.16)	0.09	(0.15)	0.07	(0.15)	0.15	(0.11)	0.12	(0.11)
Secondary	0.44**	(0.15)	0.40**	(0.15)	0.36*	(0.16)	0.32*	(0.16)	0.19	(0.16)	0.16	(0.16)	0.27	(0.15)	0.25	(0.15)	0.31**	(0.11)	0.28**	(0.11)
University	0.37	(0.21)	0.35	(0.21)	0.52*	(0.22)	0.50*	(0.22)	0.28	(0.23)	0.26	(0.23)	0.13	(0.22)	0.11	(0.22)	0.32*	(0.15)	0.30*	(0.15)
Childhood amenities	0.00	(0.02)	0.00	(0.02)	0.01	(0.02)	0.01	(0.02)	0.02	(0.02)	0.02	(0.02)	0.00	(0.02)	0.00	(0.02)	0.01	(0.01)	0.01	(0.01)
Education																				
Primary	0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00	
Secondary	0.57***	(0.11)	0.56***	(0.11)	0.40***	(0.11)	0.38***	(0.11)	0.53***	(0.12)	0.53***	(0.12)	0.34**	(0.11)	0.35**	(0.11)	0.46***	(0.08)	0.46***	(0.08)
University	1.00***	(0.12)	0.98***	(0.12)	0.74***	(0.12)	0.71***	(0.12)	0.82***	(0.12)	0.81***	(0.13)	0.69***	(0.12)	0.70***	(0.12)	0.81***	(0.08)	0.80***	(0.08)
Household assets	0.05***	(0.01)	0.04***	(0.01)	0.05***	(0.01)	0.04***	(0.01)	0.03*	(0.01)	0.03*	(0.01)	0.03**	(0.01)	0.03**	(0.01)	0.04***	(0.01)	0.04***	(0.01)
Novosibirsk (n=2,655)																				
Mother's education																				
Less than primary	0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00	
Primary	0.03	(0.05)	0.03	(0.05)	0.03	(0.05)	0.02	(0.05)	0.14**	(0.05)	0.14**	(0.05)	0.07	(0.05)	0.07	(0.05)	0.07	(0.03)	0.07	(0.03)
Secondary	0.09	(0.05)	0.09	(0.05)	0.08	(0.05)	0.07	(0.05)	0.05	(0.05)	0.05	(0.05)	0.10*	(0.05)	0.10*	(0.05)	0.08*	(0.04)	0.08*	(0.04)
University	0.19*	(0.08)	0.19*	(0.08)	0.25**	(0.09)	0.25**	(0.09)	0.18*	(0.09)	0.17	(0.09)	0.17*	(0.08)	0.17*	(0.08)	0.20***	(0.06)	0.20***	(0.06)
Childhood amenities	0.03**	(0.01)	0.03**	(0.01)	-0.02*	(0.01)	-0.02*	(0.01)	0.00	(0.01)	0.00	(0.01)	0.01	(0.01)	0.01	(0.01)	0.01	(0.01)	0.01	(0.01)
Education																				
Primary	0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00	
Secondary	0.20***	(0.06)	0.19**	(0.06)	0.05	(0.06)	0.04	(0.06)	0.24***	(0.06)	0.24***	(0.06)	0.25***	(0.06)	0.25***	(0.06)	0.18***	(0.04)	0.18***	(0.04)
University	0.47***	(0.06)	0.45***	(0.06)	0.35***	(0.07)	0.35***	(0.07)	0.61***	(0.07)	0.59***	(0.07)	0.45***	(0.06)	0.44***	(0.06)	0.47***	(0.05)	0.46***	(0.05)
Household assets	0.05***	(0.01)	0.05***	(0.01)	0.08***	(0.01)	0.08***	(0.01)	0.07***	(0.01)	0.06***	(0.01)	0.05***	(0.01)	0.05***	(0.01)	0.06***	(0.01)	0.06***	(0.01)
Krakow (n=3,567)																				
Mother's education																				
Less than primary	0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00	
Primary	0.12*	(0.05)	0.12*	(0.05)	0.07	(0.05)	0.06	(0.05)	0.22***	(0.05)	0.21***	(0.05)	0.09	(0.05)	0.08	(0.05)	0.12***	(0.04)	0.11**	(0.04)
Secondary	0.21***	(0.06)	0.20***	(0.06)	0.17**	(0.06)	0.16**	(0.06)	0.26***	(0.06)	0.25***	(0.06)	0.11	(0.06)	0.11	(0.06)	0.19***	(0.04)	0.18***	(0.04)
University	0.24**	(0.09)	0.24**	(0.09)	0.24*	(0.09)	0.24**	(0.09)	0.48***	(0.10)	0.48***	(0.10)	0.12	(0.10)	0.12	(0.10)	0.27***	(0.07)	0.27***	(0.07)
Childhood amenities	0.01	(0.01)	0.01	(0.01)	0.02*	(0.01)	0.03**	(0.01)	0.03**	(0.01)	0.03**	(0.01)	0.01	(0.01)	0.01	(0.01)	0.02**	(0.01)	0.02**	(0.01)
Education																				
Primary	0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00	
Secondary	0.29***	(0.05)	0.28***	(0.05)	0.24***	(0.06)	0.23***	(0.06)	0.17**	(0.06)	0.16**	(0.06)	0.19***	(0.06)	0.18**	(0.06)	0.22***	(0.04)	0.21***	(0.04)
University	0.70***	(0.06)	0.68***	(0.06)	0.59***	(0.06)	0.56***	(0.06)	0.46***	(0.07)	0.44***	(0.07)	0.47***	(0.06)	0.44***	(0.07)	0.55***	(0.05)	0.53***	(0.05)
Household assets	0.06***	(0.01)	0.05***	(0.01)	0.06***	(0.01)	0.05***	(0.01)	0.07***	(0.01)	0.06***	(0.01)	0.06***	(0.01)	0.05***	(0.01)	0.06***	(0.01)	0.06***	(0.01)
Kaunas (n=2,790)																				
Mother's education																				
Less than primary	0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00	
Primary	0.08	(0.05)	0.07	(0.05)	-0.04	(0.05)	-0.05	(0.05)	0.14**	(0.05)	0.14**	(0.05)	0.02	(0.05)	0.02	(0.05)	0.05	(0.03)	0.05	(0.03)
Secondary	0.16**	(0.06)	0.16**	(0.06)	0.01	(0.06)	0.01	(0.06)	0.23***	(0.06)	0.24***	(0.06)	0.07	(0.06)	0.07	(0.06)	0.12**	(0.04)	0.12**	(0.04)
University	0.12	(0.09)	0.13	(0.09)	0.12	(0.09)	0.13	(0.09)	0.46***	(0.09)	0.46***	(0.09)	0.01	(0.09)	0.02	(0.09)	0.18**	(0.06)	0.18**	(0.06)
Childhood amenities	-0.01	(0.02)	-0.01	(0.02)	-0.03	(0.02)	-0.03	(0.02)	0.01	(0.02)	0.01	(0.02)	-0.02	(0.02)	-0.02	(0.02)	-0.01	(0.01)	-0.01	(0.01)
Education																				
Primary	0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00	
Secondary	0.43***	(0.06)	0.43***	(0.06)	0.29***	(0.06)	0.30***	(0.06)	0.40***	(0.06)	0.39***	(0.06)	0.41***	(0.06)	0.41***	(0.06)	0.38***	(0.04)	0.38***	(0.04)
University	0.79***	(0.06)	0.79***	(0.06)	0.68***	(0.06)	0.68***	(0.07)	0.82***	(0.06)	0.80***	(0.06)	0.72***	(0.06)	0.71***	(0.06)	0.75***	(0.04)	0.75***	(0.04)
Household assets	0.05***	(0.01)	0.05***	(0.01)	0.02*	(0.01)	0.02*	(0.01)	0.04***	(0.01)	0.04***	(0.01)	0.03***	(0.01)	0.03**	(0.01)	0.04***	(0.01)	0.03***	(0.01)

b=regression coefficient; SE=standard error

Model 1: Adjusted for age and measurement wave.

Model 2: Adjusted for alcohol intake, smoking status, age and measurement wave.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table III-4 Results for mutually-adjusted and health-behaviours adjusted regression models of life course SEP and cognitive function in women

	Word recall				Verbal fluency				Letter search				Delayed recall				Global cognition			
	Mutually adjusted		Health behaviours		Mutually adjusted		Health behaviours		Mutually adjusted		Health behaviours		Mutually adjusted		Health behaviours		Mutually adjusted		Health behaviours	
	b	SE	b	SE	b	SE	b	SE	b	SE	b	SE	b	SE	b	SE	b	SE	b	SE
Czech towns (n=2,376)																				
Mother's education																				
Less than primary	0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00	
Primary	0.36**	(0.12)	0.34**	(0.12)	0.19	(0.12)	0.19	(0.12)	0.29*	(0.13)	0.29*	(0.13)	0.39**	(0.13)	0.37**	(0.13)	0.31***	(0.08)	0.30***	(0.08)
Secondary	0.51***	(0.12)	0.49***	(0.12)	0.37**	(0.12)	0.37**	(0.12)	0.35**	(0.13)	0.36**	(0.13)	0.49***	(0.13)	0.47***	(0.13)	0.43***	(0.09)	0.42***	(0.09)
University	0.57**	(0.22)	0.56*	(0.22)	0.52*	(0.22)	0.51*	(0.22)	0.41	(0.24)	0.42	(0.24)	0.65**	(0.23)	0.63**	(0.23)	0.54***	(0.15)	0.53***	(0.15)
Childhood amenities	-0.01	(0.02)	-0.00	(0.02)	-0.01	(0.02)	-0.01	(0.02)	0.02	(0.02)	0.02	(0.02)	-0.01	(0.02)	-0.01	(0.02)	-0.00	(0.01)	-0.00	(0.01)
Education																				
Primary	0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00	
Secondary	0.67***	(0.06)	0.66***	(0.06)	0.59***	(0.06)	0.58***	(0.06)	0.27***	(0.06)	0.25***	(0.06)	0.46***	(0.06)	0.44***	(0.06)	0.50***	(0.04)	0.48***	(0.04)
University	0.97***	(0.08)	0.94***	(0.08)	1.13***	(0.08)	1.13***	(0.08)	0.46***	(0.08)	0.44***	(0.08)	0.74***	(0.08)	0.72***	(0.08)	0.83***	(0.05)	0.81***	(0.05)
Household assets	0.04**	(0.01)	0.03**	(0.01)	0.02	(0.01)	0.02	(0.01)	0.03*	(0.01)	0.02	(0.01)	0.02*	(0.01)	0.02	(0.01)	0.03***	(0.01)	0.02**	(0.01)
Novosibirsk (n=3,285)																				
Mother's education																				
Less than primary	0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00	
Primary	0.14***	(0.04)	0.14***	(0.04)	0.12**	(0.04)	0.11*	(0.04)	0.01	(0.05)	0.00	(0.05)	0.15***	(0.04)	0.15***	(0.04)	0.10***	(0.03)	0.10***	(0.03)
Secondary	0.24***	(0.04)	0.24***	(0.04)	0.24***	(0.05)	0.23***	(0.05)	-0.01	(0.05)	-0.01	(0.05)	0.24***	(0.04)	0.23***	(0.04)	0.18***	(0.03)	0.17***	(0.03)
University	0.21**	(0.08)	0.22**	(0.08)	0.30***	(0.08)	0.29***	(0.08)	-0.06	(0.09)	-0.05	(0.09)	0.27***	(0.08)	0.27***	(0.08)	0.18**	(0.06)	0.18***	(0.05)
Childhood amenities	0.04***	(0.01)	0.04***	(0.01)	-0.01	(0.01)	-0.01	(0.01)	0.03**	(0.01)	0.03**	(0.01)	0.02*	(0.01)	0.02*	(0.01)	0.02**	(0.01)	0.02**	(0.01)
Education																				
Primary	0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00	
Secondary	0.30***	(0.05)	0.30***	(0.05)	0.20***	(0.06)	0.20***	(0.06)	0.32***	(0.06)	0.32***	(0.06)	0.23***	(0.05)	0.23***	(0.05)	0.26***	(0.04)	0.26***	(0.04)
University	0.62***	(0.06)	0.62***	(0.06)	0.56***	(0.07)	0.56***	(0.07)	0.50***	(0.07)	0.50***	(0.07)	0.47***	(0.06)	0.47***	(0.06)	0.54***	(0.04)	0.54***	(0.04)
Household assets	0.04***	(0.01)	0.04***	(0.01)	0.06***	(0.01)	0.06***	(0.01)	0.06***	(0.01)	0.06***	(0.01)	0.04***	(0.01)	0.04***	(0.01)	0.05***	(0.01)	0.05***	(0.01)
Krakow (n=3,778)																				
Mother's education																				
Less than primary	0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00	
Primary	0.08	(0.05)	0.07	(0.05)	0.21***	(0.05)	0.20***	(0.05)	0.31***	(0.05)	0.30***	(0.05)	0.08	(0.05)	0.08	(0.05)	0.17***	(0.04)	0.16***	(0.04)
Secondary	0.12*	(0.05)	0.11*	(0.05)	0.35***	(0.06)	0.33***	(0.06)	0.28***	(0.06)	0.27***	(0.06)	0.06	(0.06)	0.05	(0.06)	0.20***	(0.04)	0.19***	(0.04)
University	0.18*	(0.09)	0.16	(0.09)	0.48***	(0.09)	0.47***	(0.09)	0.36***	(0.10)	0.35***	(0.10)	0.16	(0.09)	0.16	(0.09)	0.30***	(0.07)	0.28***	(0.07)
Childhood amenities	0.02	(0.01)	0.01	(0.01)	0.02	(0.01)	0.01	(0.01)	0.03**	(0.01)	0.03**	(0.01)	0.01	(0.01)	0.01	(0.01)	0.02**	(0.01)	0.02*	(0.01)
Education																				
Primary	0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00	
Secondary	0.39***	(0.04)	0.38***	(0.04)	0.28***	(0.05)	0.26***	(0.05)	0.32***	(0.05)	0.30***	(0.05)	0.33***	(0.05)	0.32***	(0.05)	0.33***	(0.03)	0.31***	(0.03)
University	0.79***	(0.05)	0.73***	(0.05)	0.71***	(0.05)	0.65***	(0.05)	0.54***	(0.06)	0.50***	(0.06)	0.67***	(0.06)	0.63***	(0.06)	0.68***	(0.04)	0.63***	(0.04)
Household assets	0.04***	(0.01)	0.03***	(0.01)	0.01	(0.01)	0.01	(0.01)	0.04***	(0.01)	0.04***	(0.01)	0.02**	(0.01)	0.02*	(0.01)	0.03***	(0.01)	0.02***	(0.01)
Kaunas (n=3,389)																				
Mother's education																				
Less than primary	0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00	
Primary	0.11**	(0.04)	0.11**	(0.04)	0.07	(0.04)	0.07	(0.04)	0.02	(0.04)	0.01	(0.04)	0.01	(0.04)	0.00	(0.04)	0.05	(0.03)	0.05	(0.03)
Secondary	0.15**	(0.05)	0.15**	(0.05)	0.07	(0.05)	0.07	(0.05)	0.10	(0.05)	0.10	(0.05)	0.09	(0.05)	0.09	(0.05)	0.10**	(0.04)	0.10**	(0.04)
University	0.21*	(0.08)	0.22**	(0.08)	0.28**	(0.09)	0.29**	(0.09)	-0.07	(0.09)	-0.06	(0.09)	0.04	(0.09)	0.05	(0.09)	0.12	(0.06)	0.12*	(0.06)
Childhood amenities	-0.02	(0.01)	-0.02	(0.01)	-0.00	(0.01)	-0.00	(0.01)	0.00	(0.01)	0.00	(0.02)	-0.03	(0.01)	-0.03	(0.01)	-0.01	(0.01)	-0.01	(0.01)
Education																				
Primary	0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00	
Secondary	0.58***	(0.05)	0.58***	(0.05)	0.35***	(0.06)	0.35***	(0.06)	0.52***	(0.06)	0.51***	(0.06)	0.57***	(0.06)	0.57***	(0.06)	0.51***	(0.04)	0.50***	(0.04)
University	0.97***	(0.06)	0.96***	(0.06)	0.83***	(0.06)	0.82***	(0.06)	0.88***	(0.06)	0.87***	(0.06)	0.89***	(0.06)	0.89***	(0.06)	0.89***	(0.04)	0.88***	(0.04)
Household assets	0.04***	(0.01)	0.04***	(0.01)	0.01	(0.01)	0.01	(0.01)	0.04***	(0.01)	0.04***	(0.01)	0.03***	(0.01)	0.03***	(0.01)	0.03***	(0.01)	0.03***	(0.01)

b=regression coefficient; SE=standard error

Model 1: Adjusted for age and measurement wave.

Model 2: Adjusted for alcohol intake, smoking status, age and measurement wave.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table III-5 Results for fully adjusted regression models of life course SEP and cognitive function in men

	Word recall		Verbal fluency		Letter search		Delayed recall		Global cognition	
	b	SE	b	SE	b	SE	b	SE	b	SE
Czech towns (n=2,048)										
Mother's education										
Less than primary	0.00		0.00		0.00		0.00		0.00	
Primary	0.22	(0.15)	0.16	(0.16)	0.03	(0.16)	0.06	(0.15)	0.12	(0.11)
Secondary	0.39*	(0.15)	0.33*	(0.16)	0.13	(0.16)	0.23	(0.15)	0.27*	(0.11)
University	0.30	(0.21)	0.47*	(0.23)	0.19	(0.23)	0.07	(0.22)	0.26	(0.15)
Childhood amenities	-0.00	(0.02)	0.01	(0.02)	0.01	(0.02)	-0.00	(0.02)	0.00	(0.01)
Education										
Primary	0.00		0.00		0.00		0.00		0.00	
Secondary	0.55***	(0.11)	0.38**	(0.11)	0.52***	(0.12)	0.35**	(0.11)	0.45***	(0.08)
University	0.96***	(0.12)	0.70***	(0.12)	0.79***	(0.12)	0.69***	(0.12)	0.78***	(0.08)
Household assets	0.04***	(0.01)	0.04***	(0.01)	0.03*	(0.01)	0.03*	(0.01)	0.03***	(0.01)
Novosibirsk (n=2,655)										
Mother's education										
Less than primary	0.00		0.00		0.00		0.00		0.00	
Primary	0.02	(0.05)	0.02	(0.05)	0.15**	(0.05)	0.07	(0.05)	0.06	(0.03)
Secondary	0.08	(0.05)	0.07	(0.05)	0.04	(0.05)	0.10*	(0.05)	0.07*	(0.04)
University	0.17*	(0.08)	0.24**	(0.09)	0.16	(0.09)	0.16*	(0.08)	0.18**	(0.06)
Childhood amenities	0.03**	(0.01)	-0.02	(0.01)	0.01	(0.01)	0.01	(0.01)	0.01	(0.01)
Education										
Primary	0.00		0.00		0.00		0.00		0.00	
Secondary	0.18**	(0.06)	0.05	(0.06)	0.23***	(0.06)	0.24***	(0.06)	0.17***	(0.04)
University	0.43***	(0.06)	0.34***	(0.07)	0.57***	(0.07)	0.43***	(0.06)	0.44***	(0.04)
Household assets	0.04***	(0.01)	0.08***	(0.01)	0.06***	(0.01)	0.04***	(0.01)	0.05***	(0.01)
Krakow (n=3,567)										
Mother's education										
Less than primary	0.00		0.00		0.00		0.00		0.00	
Primary	0.11*	(0.05)	0.06	(0.05)	0.20***	(0.05)	0.08	(0.05)	0.11**	(0.04)
Secondary	0.20***	(0.06)	0.16**	(0.06)	0.24***	(0.06)	0.10	(0.06)	0.18***	(0.04)
University	0.25**	(0.09)	0.25**	(0.09)	0.48***	(0.10)	0.13	(0.10)	0.28***	(0.07)
Childhood amenities	0.01	(0.01)	0.03**	(0.01)	0.03**	(0.01)	0.01	(0.01)	0.02**	(0.01)
Education										
Primary	0.00		0.00		0.00		0.00		0.00	
Secondary	0.28***	(0.05)	0.22***	(0.06)	0.16**	(0.06)	0.18**	(0.06)	0.21***	(0.04)
University	0.66***	(0.06)	0.55***	(0.06)	0.43***	(0.07)	0.42***	(0.07)	0.52***	(0.05)
Household assets	0.05***	(0.01)	0.05***	(0.01)	0.06***	(0.01)	0.05***	(0.01)	0.05***	(0.01)
Kaunas (n=2,790)										
Mother's education										
Less than primary	0.00		0.00		0.00		0.00		0.00	
Primary	0.08	(0.05)	-0.04	(0.05)	0.14**	(0.05)	0.02	(0.05)	0.05	(0.03)
Secondary	0.16**	(0.06)	0.01	(0.06)	0.24***	(0.06)	0.06	(0.06)	0.12**	(0.04)
University	0.12	(0.09)	0.12	(0.09)	0.46***	(0.09)	0.01	(0.09)	0.18**	(0.06)
Childhood amenities	-0.01	(0.02)	-0.03	(0.02)	0.01	(0.02)	-0.02	(0.02)	-0.01	(0.01)
Education										
Primary	0.00		0.00		0.00		0.00		0.00	
Secondary	0.43***	(0.06)	0.29***	(0.06)	0.39***	(0.06)	0.41***	(0.06)	0.38***	(0.04)
University	0.78***	(0.06)	0.66***	(0.06)	0.80***	(0.06)	0.70***	(0.06)	0.74***	(0.04)
Household assets	0.04***	(0.01)	0.01	(0.01)	0.03***	(0.01)	0.03**	(0.01)	0.03***	(0.01)

b=regression coefficient; SE-=standard error

Adjusted for age, alcohol intake, smoking status, self-rated health and self-reported medical history (MI, angina/IHD, stroke, hypertension, and diabetes) and measurement wave.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table III-6 Results for fully adjusted regression models of life course SEP and cognitive function in women

	Word recall		Verbal fluency		Letter search		Delayed recall		Global cognition	
	b	SE	b	SE	b	SE	b	SE	b	SE
Czech towns (n=2,376)										
Mother's education										
Less than primary	0.00		0.00		0.00		0.00		0.00	
Primary	0.35**	(0.12)	0.20	(0.12)	0.30*	(0.13)	0.37**	(0.13)	0.30***	(0.08)
Secondary	0.49***	(0.12)	0.37**	(0.12)	0.35**	(0.13)	0.46***	(0.13)	0.42***	(0.09)
University	0.56*	(0.22)	0.50*	(0.22)	0.41	(0.24)	0.62**	(0.23)	0.52***	(0.15)
Childhood amenities	-0.01	(0.02)	-0.01	(0.02)	0.02	(0.02)	-0.01	(0.02)	-0.00	(0.01)
Education										
Primary	0.00		0.00		0.00		0.00		0.00	
Secondary	0.65***	(0.06)	0.56***	(0.06)	0.24***	(0.06)	0.44***	(0.06)	0.47***	(0.04)
University	0.93***	(0.08)	1.08***	(0.08)	0.41***	(0.08)	0.70***	(0.08)	0.78***	(0.05)
Household assets	0.03**	(0.01)	0.01	(0.01)	0.02	(0.01)	0.02	(0.01)	0.02**	(0.01)
Novosibirsk (n=3,285)										
Mother's education										
Less than primary	0.00		0.00		0.00		0.00		0.00	
Primary	0.14***	(0.04)	0.12**	(0.04)	0.00	(0.05)	0.15***	(0.04)	0.10***	(0.03)
Secondary	0.24***	(0.04)	0.24***	(0.05)	-0.00	(0.05)	0.24***	(0.04)	0.18***	(0.03)
University	0.22**	(0.08)	0.29***	(0.08)	-0.05	(0.09)	0.28***	(0.08)	0.19***	(0.05)
Childhood amenities	0.04***	(0.01)	-0.01	(0.01)	0.03**	(0.01)	0.02	(0.01)	0.02**	(0.01)
Education										
Primary	0.00		0.00		0.00		0.00		0.00	
Secondary	0.30***	(0.05)	0.20**	(0.06)	0.32***	(0.06)	0.22***	(0.05)	0.26***	(0.04)
University	0.60***	(0.06)	0.55***	(0.07)	0.48***	(0.07)	0.46***	(0.06)	0.52***	(0.04)
Household assets	0.03***	(0.01)	0.06***	(0.01)	0.06***	(0.01)	0.04***	(0.01)	0.05***	(0.01)
Krakow (n=3,778)										
Mother's education										
Less than primary	0.00		0.00		0.00		0.00		0.00	
Primary	0.08	(0.05)	0.21***	(0.05)	0.31***	(0.05)	0.09	(0.05)	0.17***	(0.04)
Secondary	0.12*	(0.05)	0.34***	(0.06)	0.28***	(0.06)	0.07	(0.06)	0.20***	(0.04)
University	0.17*	(0.08)	0.47***	(0.09)	0.35***	(0.10)	0.16	(0.09)	0.29***	(0.07)
Childhood amenities	0.01	(0.01)	0.01	(0.01)	0.03**	(0.01)	0.01	(0.01)	0.02*	(0.01)
Education										
Primary	0.00		0.00		0.00		0.00		0.00	
Secondary	0.37***	(0.04)	0.24***	(0.05)	0.29***	(0.05)	0.31***	(0.05)	0.30***	(0.03)
University	0.71***	(0.05)	0.62***	(0.05)	0.47***	(0.06)	0.61***	(0.06)	0.60***	(0.04)
Household assets	0.03***	(0.01)	0.00	(0.01)	0.03***	(0.01)	0.01	(0.01)	0.02**	(0.01)
Kaunas (n=3,389)										
Mother's education										
Less than primary	0.00		0.00		0.00		0.00		0.00	
Primary	0.11**	(0.04)	0.07	(0.04)	0.01	(0.04)	0.00	(0.04)	0.05	(0.03)
Secondary	0.14**	(0.05)	0.06	(0.05)	0.10	(0.05)	0.08	(0.05)	0.10**	(0.04)
University	0.23**	(0.08)	0.30***	(0.09)	-0.05	(0.09)	0.06	(0.09)	0.13*	(0.06)
Childhood amenities	-0.02	(0.01)	-0.01	(0.01)	-0.00	(0.01)	-0.03*	(0.01)	-0.02	(0.01)
Education										
Primary	0.00		0.00		0.00		0.00		0.00	
Secondary	0.58***	(0.05)	0.36***	(0.06)	0.52***	(0.06)	0.57***	(0.06)	0.50***	(0.04)
University	0.93***	(0.06)	0.80***	(0.06)	0.85***	(0.06)	0.86***	(0.06)	0.86***	(0.04)
Household assets	0.04***	(0.01)	0.01	(0.01)	0.04***	(0.01)	0.03***	(0.01)	0.03***	(0.01)

b=regression coefficient; SE-=standard error

Adjusted for age, alcohol intake, smoking status, self-rated health and self-reported medical history (MI, angina/IHD, stroke, hypertension, and diabetes) and measurement wave.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix IV. Measurement invariance testing for SEM model

Table IV-1 Goodness of fit for selected measurement invariance imposed across all groups

Model	χ^2	df	RMSEA	TLI	CFI	n
Invariance constraints over study centres (same constraints over all four groups)						
None (all parameters free)			Just-identified; perfect fit			
Factor loading invariance						
All participants	98.538	6	0.046 [0.038-0.054]	0.986	0.993	29,073
Men only	41.831	6	0.042 [0.031-0.055]	0.988	0.994	13,420
Women only	60.325	6	0.048 [0.031-0.059]	0.985	0.992	15,653
Universal invariance constraints (same constraints over all eight groups; centre*gender)						
None (all parameters free)			Just-identified; perfect fit			
Factor loading invariance	102.27	14	0.042 [0.034-0.049]	0.989	0.993	29,073
Intercept invariance	3234.928	28	0.178 [0.172-0.183]	0.795	0.761	29,073

Abbreviations: df=degrees of freedom; RMSEA=Root mean square error of approximation; TLI=Tucker-Lewis Index; CFI=Comparative fit index; n=sample size.

Appendix V. SEM results for father's education

Table V-1 Results for father's education based on the unconstrained multiple-group structural equation model

	Czech towns				Novosibirsk				Krakow				Kaunas			
	b	**SE**	**p-value**	**Std**	**b**	**SE**	**p-value**	**Std**	**b**	**SE**	**p-value**	**Std**	**b**	**SE**	**p-value**	**Std**
Men																
Father's education																
Direct effect on cognition	0.27	0.11	0.016	0.11	-0.02	0.07	0.770	-0.01	0.30	0.08	<0.001	0.10	0.06	0.07	0.401	0.02
Direct effect on household assets	0.12	0.07	0.074	0.12	0.14	0.04	<0.001	0.14	0.01	0.04	0.765	0.01	0.07	0.05	0.166	0.07
Direct effect on education	0.40	0.05	<0.001	0.40	0.46	0.02	<0.001	0.46	0.55	0.02	<0.001	0.55	0.43	0.03	<0.001	0.43
Indirect effects of father's education on cognition via																
Education	0.38	0.05	<0.001	0.09	0.40	0.04	<0.001	0.12	0.50	0.04	<0.001	0.13	0.51	0.04	<0.001	0.17
Assets	0.01	0.01	0.124	0.00	0.04	0.01	0.001	0.01	0.00	0.01	0.766	0.00	0.01	0.01	0.194	0.00
Education and assets	0.02	0.01	0.003	0.01	0.07	0.01	<0.001	0.02	0.10	0.01	<0.001	0.03	0.02	0.01	<0.001	0.01
Total indirect effect of father's education on cognition	0.42	0.05	<0.001	0.10	0.51	0.04	<0.001	0.15	0.60	0.04	<0.001	0.16	0.54	0.04	<0.001	0.18
Total effect of father's education on cognition	0.68	0.11	<0.001	0.16	0.49	0.07	<0.001	0.14	0.90	0.07	<0.001	0.24	0.60	0.07	<0.001	0.19
N	**2,475**				**3,842**				**5,028**				**2,930**			
Women																
Father's education																
Direct effect on cognition	0.42	0.09	<0.001	0.19	0.20	0.06	0.001	0.07	0.38	0.08	<0.001	0.12	0.01	0.06	0.808	0.01
Direct effect on household assets	0.07	0.06	0.268	0.07	0.18	0.04	<0.001	0.18	0.06	0.04	0.189	0.06	0.13	0.04	0.004	0.13
Direct effect on education	0.53	0.04	<0.001	0.53	0.40	0.02	<0.001	0.40	0.63	0.03	<0.001	0.63	0.45	0.03	<0.001	0.45
Indirect effects of father's education on cognition via																
Education	0.54	0.05	<0.001	0.14	0.32	0.03	<0.001	0.10	0.62	0.04	<0.001	0.16	0.54	0.04	<0.001	0.17
Assets	0.00	0.00	0.349	0.00	0.04	0.01	<0.001	0.01	0.01	0.01	0.217	0.00	0.01	0.01	0.026	0.00
Education and assets	0.01	0.01	0.052	0.00	0.04	0.01	<0.001	0.01	0.03	0.01	<0.001	0.01	0.02	0.01	<0.001	0.01
Total indirect effect of father's education on cognition	0.56	0.05	<0.001	0.15	0.41	0.03	<0.001	0.12	0.66	0.04	<0.001	0.17	0.57	0.04	<0.001	0.18
Total effect of father's education on cognition	0.98	0.09	<0.001	0.25	0.60	0.06	<0.001	0.18	1.04	0.07	<0.001	0.27	0.59	0.06	<0.001	0.18
N	**2,935**				**4,576**				**5,267**				**3,489**			

Fit indices: χ^2 (94) = 611.923, RMSEA=0.038 [0.035-0.041]; CFI=0.979; TLI=0.956

Model estimation: WLSMV with missing data (pairwise present)

b=unstandardized regression coefficient; SE=standard error; Std=standardized beta regression coefficient

Paths from mother's education and childhood amenities to education are probit coefficients.

Appendix VI. Supplementary analyses of alcohol and cognitive function

These analyses are additionally adjusted for physical activity and depressive symptoms (Table VI-1).

Table VI-1 Results from additionally adjusted regression analyses of alcohol indices and cognitive function

	Word recall		Verbal fluency		Letter search		Delayed recall		Global cognition	
	b	SE	b	SE	b	SE	b	SE	b	SE
Men (n=12,080)										
Drinking frequency										
Never	-0.12***	(0.03)	-0.13***	(0.03)	-0.07	(0.03)	-0.09**	(0.03)	-0.10***	(0.02)
<1 /month	0.00		0.00		0.00		0.00		0.00	
1-3 /month	0.00	(0.03)	-0.00	(0.03)	0.02	(0.03)	-0.03	(0.03)	-0.00	(0.02)
3-4 /week	0.02	(0.03)	0.04	(0.03)	-0.01	(0.03)	-0.01	(0.03)	0.01	(0.02)
5+ /week	0.04	(0.03)	0.05	(0.03)	-0.00	(0.03)	-0.02	(0.03)	0.02	(0.02)
Alcohol intake (per day)										
Non-drinker	-0.13***	(0.03)	-0.14***	(0.03)	-0.08**	(0.03)	-0.08**	(0.03)	-0.11***	(0.02)
<10 g	0.00		0.00		0.00		0.00		0.00	
10-40 g	0.03	(0.02)	0.05*	(0.02)	-0.02	(0.02)	0.01	(0.02)	0.02	(0.01)
>40 g	-0.03	(0.03)	-0.05	(0.04)	-0.10**	(0.04)	-0.08*	(0.04)	-0.06*	(0.03)
Women (n=14,250)										
Drinking frequency										
Never	-0.14***	(0.02)	-0.13***	(0.02)	-0.10***	(0.02)	-0.11***	(0.02)	-0.12***	(0.02)
<1 /month	0.00		0.00		0.00		0.00		0.00	
1-3 /month	0.09***	(0.02)	0.04*	(0.02)	0.05*	(0.02)	0.06**	(0.02)	0.06***	(0.01)
3-4 /week	0.06*	(0.02)	0.04	(0.03)	0.03	(0.03)	0.07**	(0.03)	0.05**	(0.02)
5+ /week	0.12*	(0.05)	0.14**	(0.05)	-0.02	(0.05)	0.10*	(0.05)	0.08*	(0.04)
Alcohol intake (per day)										
Non-drinker	-0.17***	(0.02)	-0.15***	(0.02)	-0.12***	(0.02)	-0.13***	(0.02)	-0.14***	(0.01)
<5 g	0.00		0.00		0.00		0.00		0.00	
5-20 g	0.03	(0.02)	0.03	(0.02)	0.01	(0.02)	0.05*	(0.02)	0.03	(0.02)
>20 g	0.05	(0.04)	0.07	(0.04)	-0.07	(0.05)	0.06	(0.05)	0.03	(0.03)

b=regression coefficient; SE=standard error.
Adjusted for age, education, assets, smoking, self-rated health, self-reported medical history, physical activity, depressive symptoms and measurement wave.
Reference group is light or infrequent drinker.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

In addition, analyses were also adjusted for vascular factors from the baseline clinical examination. Not all participants, who completed the health questionnaire, attended the clinical examination, and thus these analyses are based on a smaller sample. Because these analyses had a different sample size, regression results from complete case analyses before additional adjustments are also shown.

Table VI-2 Results from regression analyses of alcohol indices and cognitive function additionally adjusted for vascular factors

	Word recall		Verbal fluency		Letter search		Delayed recall		Global cognition	
	b	SE	b	SE	b	SE	b	SE	b	SE
Men (n=11,043)										
Model 1										
Drinking frequency										
Never	-0.13***	(0.03)	-0.12***	(0.04)	-0.05	(0.04)	-0.09**	(0.04)	-0.10***	(0.02)
<1 /month	0.00		0.00		0.00		0.00		0.00	
1-3 /month	0.01	(0.03)	0.01	(0.03)	0.02	(0.03)	-0.02	(0.03)	0.01	(0.02)
3-4 /week	0.02	(0.03)	0.05	(0.03)	-0.01	(0.03)	-0.01	(0.03)	0.02	(0.02)
5+ /week	0.06	(0.03)	0.08*	(0.03)	0.00	(0.03)	-0.00	(0.03)	0.03	(0.02)
Model 2										
Drinking frequency										
Never	-0.15***	(0.03)	-0.14***	(0.04)	-0.07	(0.04)	-0.11**	(0.04)	-0.11***	(0.02)
<1 /month	0.00		0.00		0.00		0.00		0.00	
1-3 /month	0.02	(0.03)	0.02	(0.03)	0.03	(0.03)	-0.01	(0.03)	0.01	(0.02)
3-4 /week	0.04	(0.03)	0.07*	(0.03)	0.01	(0.03)	0.01	(0.03)	0.03	(0.02)
5+ /week	0.08*	(0.03)	0.08*	(0.03)	0.02	(0.03)	0.02	(0.03)	0.05*	(0.02)
Model 1										
Alcohol intake (per day)										
Non-drinker	-0.14***	(0.03)	-0.17***	(0.03)	-0.07**	(0.03)	-0.08***	(0.03)	-0.11***	(0.02)
<10 g	0.00		0.00		0.00		0.00		0.00	
10-40 g	0.03	(0.02)	0.05*	(0.02)	-0.02	(0.02)	0.02	(0.02)	0.02	(0.01)
>40 g	-0.01	(0.04)	-0.04	(0.04)	-0.08	(0.04)	-0.05	(0.04)	-0.04	(0.03)
Model 2										
Alcohol intake (per day)										
Non-drinker	-0.14***	(0.03)	-0.14***	(0.03)	-0.07*	(0.03)	-0.09**	(0.03)	-0.11***	(0.02)
<10 g	0.00		0.00		0.00		0.00		0.00	
10-40 g	0.04*	(0.02)	0.06**	(0.02)	-0.01	(0.02)	0.02	(0.02)	0.03*	(0.01)
>40 g	0.01	(0.04)	-0.02	(0.04)	-0.06	(0.04)	-0.04	(0.04)	-0.03	(0.03)
Women (n=13,220)										
Model 1										
Drinking frequency										
Never	-0.13***	(0.02)	-0.13***	(0.02)	-0.09***	(0.02)	-0.10***	(0.02)	-0.11***	(0.02)
<1 /month	0.00		0.00		0.00		0.00		0.00	
1-3 /month	0.09***	(0.02)	0.04*	(0.02)	0.05*	(0.02)	0.07***	(0.02)	0.06***	(0.01)
3-4 /week	0.06*	(0.03)	0.05	(0.03)	0.03	(0.03)	0.07*	(0.03)	0.05**	(0.02)
5+ /week	0.14**	(0.05)	0.14**	(0.05)	-0.02	(0.06)	0.10	(0.06)	0.09*	(0.04)
Model 2										
Drinking frequency										
Never	-0.16***	(0.02)	-0.15***	(0.02)	-0.12***	(0.02)	-0.12***	(0.02)	-0.14***	(0.02)
<1 /month	0.00		0.00		0.00		0.00		0.00	
1-3 /month	0.10***	(0.02)	0.05*	(0.02)	0.05**	(0.02)	0.07***	(0.02)	0.07***	(0.01)
3-4 /week	0.07**	(0.03)	0.06*	(0.03)	0.04	(0.03)	0.07**	(0.03)	0.06***	(0.02)
5+ /week	0.15**	(0.05)	0.15**	(0.05)	-0.01	(0.06)	0.10	(0.06)	0.10*	(0.04)
Model 1										
Alcohol intake (per day)										
Non-drinker	-0.17***	(0.02)	-0.15***	(0.02)	-0.11***	(0.02)	-0.13***	(0.02)	-0.14***	(0.01)
<5 g	0.00		0.00		0.00		0.00		0.00	
5-20 g	0.03	(0.02)	0.03	(0.02)	0.01	(0.02)	0.05*	(0.02)	0.03	(0.02)
>20 g	0.07	(0.05)	0.08	(0.05)	-0.06	(0.05)	0.06	(0.05)	0.03	(0.03)
Model 2										
Alcohol intake (per day)										
Non-drinker	-0.17***	(0.02)	-0.14***	(0.02)	-0.11***	(0.02)	-0.13***	(0.02)	-0.14***	(0.02)
<5 g	0.00		0.00		0.00		0.00		0.00	
5-20 g	0.03	(0.02)	0.03	(0.02)	0.01	(0.03)	0.05*	(0.02)	0.03	(0.02)
>20 g	0.06	(0.05)	0.07	(0.05)	-0.06	(0.05)	0.06	(0.05)	0.03	(0.03)

b=regression coefficient; SE=standard error

Model 1: Adjusted for age, education, assets, smoking, self-rated health, self-reported medical history, physical activity, depressive symptoms and measurement wave.

Model 2: Additionally adjusted for vascular factors from baseline clinical examination.

Reference group is light or infrequent drinker.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix VII. Analyses of binge drinking and cognitive function

These analyses show the association between binge drinking and cognitive function in drinkers for the pooled sample, controlling for total alcohol intake.

Table VII-1 Regression estimates of cognitive function and binge drinking in drinkers

	Model 1: Age		Model 2: Education, assets		Model 3: Smoking		Model 4: Health	
	b	SE	b	SE	b	SE	b	SE
Men (n=11,034)								
Word recall								
Non-binge drinker	0.00		0.00		0.00		0.00	
Binge drinker	0.01	(0.02)	0.06*	(0.02)	0.06**	(0.02)	0.06*	(0.02)
Verbal fluency								
Non-binge drinker	0.00		0.00		0.00		0.00	
Binge drinker	-0.06*	(0.03)	-0.02	(0.02)	-0.02	(0.02)	-0.02	(0.02)
Letter cancellation								
Non-binge drinker	0.00		0.00		0.00		0.00	
Binge drinker	-0.06*	(0.03)	-0.01	(0.02)	0.00	(0.02)	-0.01	(0.02)
Delayed recall								
Non-binge drinker	0.00		0.00		0.00		0.00	
Binge drinker	0.02	(0.02)	0.06*	(0.02)	0.06*	(0.02)	0.05*	(0.02)
Global cognition								
Non-binge drinker	0.00		0.00		0.00		0.00	
Binge drinker	-0.09	(0.07)	0.09	(0.07)	0.11	(0.07)	0.08	(0.07)
Women (n=11,644)								
Word recall								
Non-binge drinker	0.00		0.00		0.00		0.00	
Binge drinker	0.02	(0.03)	0.02	(0.03)	0.02	(0.03)	0.02	(0.03)
Verbal fluency								
Non-binge drinker	0.00		0.00		0.00		0.00	
Binge drinker	-0.05	(0.03)	-0.04	(0.03)	-0.04	(0.03)	-0.05	(0.03)
Letter cancellation								
Non-binge drinker	0.00		0.00		0.00		0.00	
Binge drinker	0.01	(0.04)	0.01	(0.03)	0.02	(0.03)	0.01	(0.03)
Delayed recall								
Non-binge drinker	0.00		0.00		0.00		0.00	
Binge drinker	0.06	(0.03)	0.06	(0.03)	0.06	(0.03)	0.06	(0.03)
Global cognition								
Non-binge drinker	0.00		0.00		0.00		0.00	
Binge drinker	0.04	(0.10)	0.05	(0.09)	0.06	(0.09)	0.04	(0.09)

b=regression coefficient; SE=standard error
Model 1: Adjusted for age.
Model 2: Additionally adjusted for education and assets.
Model 3: Additionally adjusted for smoking.
Model 4: Additionally adjusted for health measures.
All models also adjusted for alcohol volume, centre and measurement wave.
Reference group is non-binge drinker.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix VIII. Sensitivity analyses of alcohol and cognitive function: Attrition

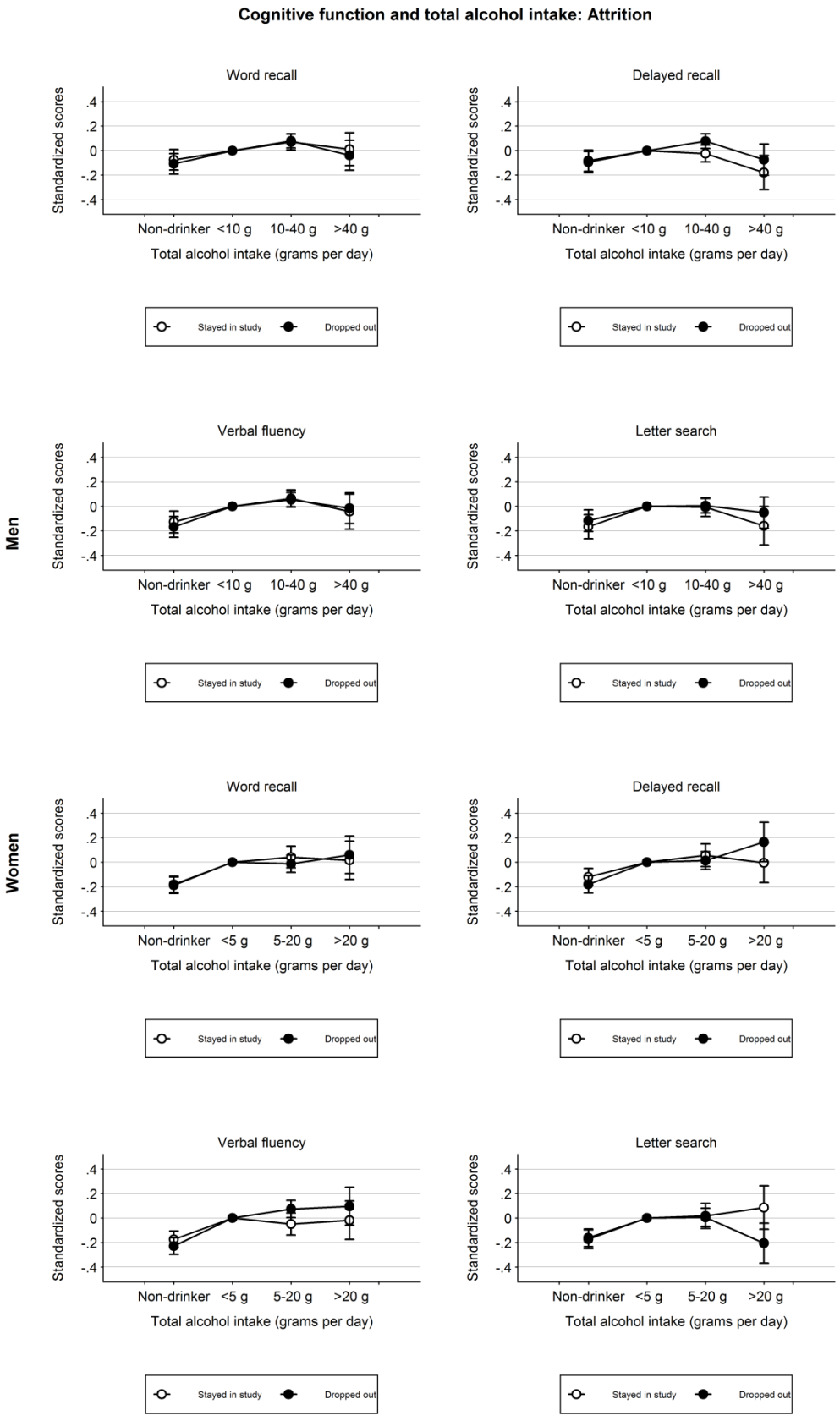

Figure VIII-1 Regression results for alcohol intake and cognitive function in participants who dropped out between baseline and follow-up compared to participants who remained in the study

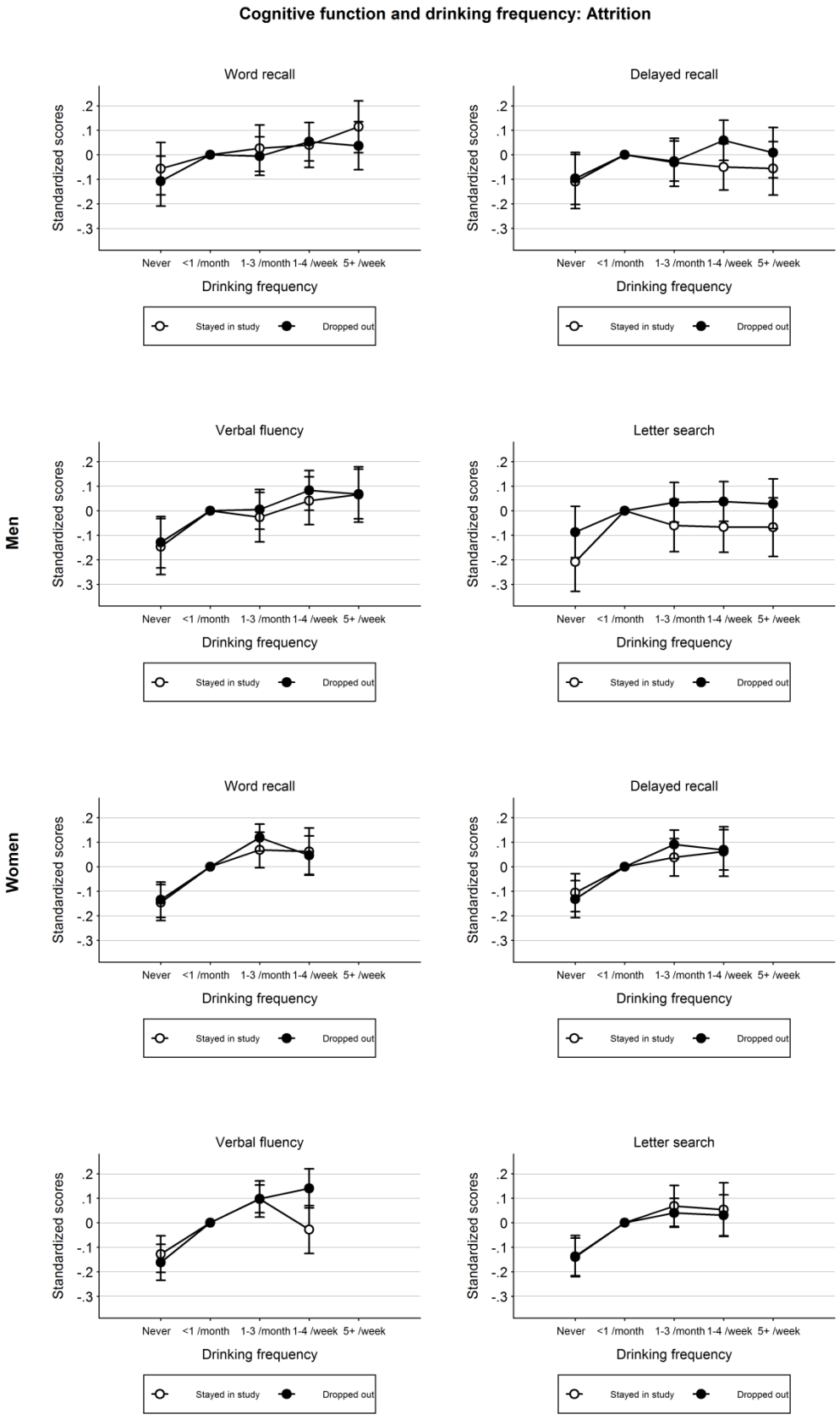

Figure VIII-2 Regression results for drinking frequency and cognitive function in participants who dropped out between baseline and follow-up compared to participants who remained in the study

Appendix IX. Health-adjusted analyses of past drinking and cognitive function in Novosibirsk

Table IX-1 Regression estimates from analyses of past alcohol use and cognitive function in Novosibirsk adjusted for health measures

	Word recall		Verbal fluency		Letter search		Delayed recall		Global cognition	
	b	SE	b	SE	b	SE	b	SE	b	SE
Men (n=2,770)										
Past use vs. frequency										
Stable non-drinker	-0.05	(0.17)	0.01	(0.18)	-0.11	(0.18)	0.05	(0.17)	-0.02	(0.12)
Former drinker - Health	-0.15	(0.08)	-0.05	(0.09)	-0.01	(0.09)	-0.12	(0.08)	-0.08	(0.06)
Former drinker - Other	0.11	(0.07)	0.13	(0.08)	-0.02	(0.08)	0.12	(0.07)	0.09	(0.05)
Stable <1 pw	0.00		0.00		0.00		0.00		0.00	
Stable ≥1 pw	0.10*	(0.05)	0.06	(0.05)	-0.08	(0.05)	0.09	(0.05)	0.05	(0.04)
Reduced use <1 pw	0.08	(0.05)	0.06	(0.05)	-0.06	(0.05)	0.14**	(0.05)	0.06	(0.04)
Reduced use ≥1 pw	0.03	(0.05)	0.11*	(0.06)	-0.10	(0.06)	0.07	(0.05)	0.03	(0.04)
Past use vs. intake										
Stable non-drinker	-0.08	(0.17)	-0.01	(0.18)	-0.09	(0.18)	0.02	(0.17)	-0.04	(0.12)
Former drinker - Health	-0.18*	(0.08)	-0.08	(0.08)	0.00	(0.09)	-0.16*	(0.08)	-0.10	(0.06)
Former drinker - Other	0.08	(0.07)	0.11	(0.08)	-0.01	(0.08)	0.08	(0.07)	0.07	(0.05)
Stable <10 g /day	0.00		0.00		0.00		0.00		0.00	
Stable 10-40 g /day	0.04	(0.05)	0.04	(0.06)	-0.00	(0.06)	0.04	(0.05)	0.03	(0.04)
Stable >40 g /day	0.09	(0.08)	-0.01	(0.09)	-0.24**	(0.09)	-0.02	(0.08)	-0.04	(0.06)
Reduced use <10 g /day	0.04	(0.05)	0.02	(0.05)	-0.07	(0.05)	0.10*	(0.04)	0.02	(0.03)
Reduced use 10-40 g /day	0.01	(0.06)	0.16**	(0.06)	-0.05	(0.06)	0.01	(0.06)	0.03	(0.04)
Reduced use >40 g /day	-0.07	(0.10)	0.01	(0.10)	-0.05	(0.11)	0.05	(0.10)	-0.02	(0.07)
Women (n=3,511)										
Past use vs. frequency										
Stable non-drinker	-0.12*	(0.05)	-0.12*	(0.06)	-0.01	(0.06)	-0.08	(0.05)	-0.08*	(0.04)
Former drinker - Health	-0.15*	(0.07)	-0.04	(0.07)	-0.01	(0.08)	-0.13	(0.07)	-0.08	(0.05)
Former drinker - Other	0.01	(0.07)	0.04	(0.07)	-0.08	(0.08)	-0.03	(0.07)	-0.01	(0.05)
Stable <1 pw	0.00		0.00		0.00		0.00		0.00	
Stable ≥1 pw	-0.04	(0.07)	0.03	(0.07)	0.06	(0.08)	0.07	(0.07)	0.03	(0.05)
Reduced use <1 pw	-0.01	(0.03)	0.08*	(0.03)	0.03	(0.04)	0.01	(0.03)	0.03	(0.02)
Reduced use ≥1 pw	0.16	(0.10)	-0.13	(0.11)	0.11	(0.12)	0.08	(0.11)	0.06	(0.08)
Past use vs. intake										
Stable non-drinker	-0.11*	(0.05)	-0.12*	(0.06)	-0.01	(0.06)	-0.08	(0.05)	-0.08*	(0.04)
Former drinker - Health	-0.14*	(0.07)	-0.05	(0.07)	-0.02	(0.08)	-0.13	(0.07)	-0.08	(0.05)
Former drinker - Other	0.01	(0.07)	0.04	(0.07)	-0.08	(0.08)	-0.02	(0.07)	-0.01	(0.05)
Stable <5 g /day	0.00		0.00		0.00		0.00		0.00	
Stable >5 g /day	-0.01	(0.06)	0.01	(0.07)	0.01	(0.07)	0.08	(0.06)	0.02	(0.05)
Reduced use <5 g /day	-0.01	(0.03)	0.08*	(0.03)	0.03	(0.04)	0.01	(0.03)	0.03	(0.02)
Reduced use >5 g /day	0.16	(0.10)	-0.13	(0.11)	0.07	(0.11)	0.12	(0.10)	0.06	(0.07)

b=coefficient; SE=standard error

Adjusted for age, education, assets, smoking, self-rated health, self-reported medical history and measurement wave.

Reference group is stable infrequent or stable light drinker.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix X. Baseline analyses of past drinking and cognition in Novosibirsk

Table X-1 Cognitive function and past alcohol use vs. current drinking in Novosibirsk (baseline only)

	Word recall		Verbal fluency		Letter search		Delayed recall		Global cognition	
	b	SE	b	SE	b	SE	b	SE	b	SE
Men (n=1,911)										
Past use vs. current drinking frequency										
Stable non-drinker	-0.01	(0.21)	0.13	(0.21)	0.05	(0.22)	0.14	(0.21)	0.08	(0.15)
Former drinker - Health	-0.25*	(0.10)	-0.10	(0.10)	-0.09	(0.11)	-0.21*	(0.10)	-0.16*	(0.07)
Former drinker - Other	0.03	(0.09)	0.07	(0.09)	-0.07	(0.10)	0.12	(0.09)	0.04	(0.07)
Stable <1 pw	0.00		0.00		0.00		0.00		0.00	
Stable >1 pw	0.08	(0.06)	0.06	(0.06)	-0.03	(0.06)	0.08	(0.06)	0.05	(0.04)
Reduced use <1 pw	-0.02	(0.06)	0.03	(0.06)	-0.05	(0.06)	0.12*	(0.06)	0.02	(0.04)
Reduced use <1 pw	-0.01	(0.06)	0.10	(0.06)	-0.08	(0.07)	0.01	(0.06)	0.01	(0.05)
Past use vs. current intake										
Stable non-drinker	-0.03	(0.21)	0.11	(0.21)	0.05	(0.22)	0.11	(0.21)	0.06	(0.15)
Former drinker - Health	-0.27**	(0.10)	-0.11	(0.10)	-0.08	(0.10)	-0.24*	(0.10)	-0.18*	(0.07)
Former drinker - Other	0.01	(0.09)	0.06	(0.09)	-0.07	(0.09)	0.08	(0.09)	0.02	(0.06)
Stable <10 g /day	0.00		0.00		0.00		0.00		0.00	
Stable 10-40 g /day	0.06	(0.06)	0.06	(0.06)	0.03	(0.07)	0.08	(0.06)	0.06	(0.05)
Stable >40 g /day	0.01	(0.11)	-0.05	(0.11)	-0.26*	(0.12)	-0.15	(0.11)	-0.11	(0.08)
Reduced use <10 g /day	-0.05	(0.05)	0.00	(0.05)	-0.08	(0.06)	0.07	(0.05)	-0.01	(0.04)
Reduced use 10-40 g /day	-0.02	(0.07)	0.14*	(0.07)	-0.02	(0.07)	-0.04	(0.07)	0.02	(0.05)
Reduced use >40 g /day	0.04	(0.18)	0.08	(0.17)	-0.01	(0.18)	0.06	(0.17)	0.04	(0.13)
Women (n=2,354)										
Past use vs. current drinking frequency										
Stable non-drinker	-0.11	(0.07)	-0.11	(0.06)	-0.01	(0.07)	-0.10	(0.07)	-0.08	(0.05)
Former drinker - Health	-0.21*	(0.08)	-0.15	(0.08)	-0.10	(0.09)	-0.17*	(0.09)	-0.16**	(0.06)
Former drinker - Other	-0.11	(0.08)	-0.11	(0.08)	-0.14	(0.09)	-0.11	(0.08)	-0.12*	(0.06)
Stable <1 pw	0.00		0.00		0.00		0.00		0.00	
Stable >1 pw	-0.05	(0.09)	0.02	(0.08)	-0.03	(0.09)	0.04	(0.09)	-0.00	(0.06)
Reduced use <1 pw	-0.01	(0.04)	0.02	(0.04)	0.07	(0.05)	0.03	(0.04)	0.03	(0.03)
Reduced use <1 pw	0.22	(0.13)	-0.24	(0.13)	0.08	(0.14)	0.10	(0.14)	0.04	(0.10)
Past use vs. current intake										
Stable non-drinker	-0.11	(0.07)	-0.11	(0.06)	-0.01	(0.07)	-0.10	(0.07)	-0.08	(0.05)
Former drinker - Health	-0.21*	(0.08)	-0.16*	(0.08)	-0.11	(0.09)	-0.17*	(0.09)	-0.16**	(0.06)
Former drinker - Other	-0.11	(0.08)	-0.11	(0.08)	-0.14	(0.09)	-0.12	(0.08)	-0.12*	(0.06)
Stable <5 g /day	0.00		0.00		0.00		0.00		0.00	
Stable >5 g /day	-0.04	(0.08)	-0.01	(0.08)	-0.06	(0.09)	0.03	(0.08)	-0.02	(0.06)
Reduced use <5 g /day	-0.01	(0.04)	0.02	(0.04)	0.07	(0.05)	0.03	(0.04)	0.03	(0.03)
Reduced use >5 g /day	0.20	(0.13)	-0.23	(0.12)	0.06	(0.14)	0.10	(0.13)	0.03	(0.09)

b=regression coefficient; SE=standard error.
Adjusted for age, education, assets and smoking.
Reference group is stable infrequent or stable light drinker.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix XI. Analyses of pack year quintiles and cognitive function

Regression analyses with pack years of smoking categorized into centre and gender-specific quintiles and cognitive performance are shown in Table XI-1 and XI-2 for men and women, respectively. Never smokers were coded as having pack years of zero and used as the reference group in regression analyses.

Table XI-1 Results from regression analyses of pack years of smoking quintiles and cognitive scores in men (n=12,003)

	Model 1: Age-adjusted		Model 2: Education, assets		Model 3: Alcohol intake		Model 4: Health measures		
	b	SE	b	SE	b	SE	b	SE	p-value
Word recall									
Never smoker	0.000		0.000		0.000		0.000		0.371
1st quitile	-0.026	(0.03)	0.009	(0.03)	0.006	(0.03)	0.015	(0.03)	
2nd quintile	-0.051	(0.03)	0.011	(0.03)	0.007	(0.03)	0.031	(0.03)	
3rd quintile	-0.112***	(0.03)	-0.021	(0.03)	-0.023	(0.03)	-0.008	(0.03)	
4th quintile	-0.106***	(0.03)	0.001	(0.03)	-0.001	(0.03)	0.018	(0.03)	
5th quintile	-0.131***	(0.02)	-0.011	(0.02)	-0.013	(0.02)	0.013	(0.02)	
Verbal fluency									
Never smoker	0.000		0.000		0.000		0.000		0.743
1st quitile	-0.010	(0.03)	0.024	(0.03)	0.020	(0.03)	0.025	(0.03)	
2nd quintile	-0.030	(0.03)	0.030	(0.03)	0.026	(0.03)	0.041	(0.03)	
3rd quintile	-0.090**	(0.03)	-0.005	(0.03)	-0.007	(0.03)	0.003	(0.03)	
4th quintile	-0.070**	(0.03)	0.030	(0.03)	0.028	(0.03)	0.040	(0.03)	
5th quintile	-0.058*	(0.03)	0.053*	(0.03)	0.052*	(0.03)	0.071**	(0.03)	
Letter search									
Never smoker	0.000		0.000		0.000		0.000		0.012
1st quitile	-0.067*	(0.03)	-0.032	(0.03)	-0.031	(0.03)	-0.024	(0.03)	
2nd quintile	-0.057	(0.03)	0.006	(0.03)	0.007	(0.03)	0.027	(0.03)	
3rd quintile	-0.158***	(0.03)	-0.068*	(0.03)	-0.065*	(0.03)	-0.053	(0.03)	
4th quintile	-0.123***	(0.03)	-0.017	(0.03)	-0.012	(0.03)	0.003	(0.03)	
5th quintile	-0.176***	(0.03)	-0.057*	(0.03)	-0.050	(0.03)	-0.027	(0.03)	
Delayed recall									
Never smoker	0.000		0.000		0.000		0.000		0.465
1st quitile	-0.041	(0.03)	-0.014	(0.03)	-0.015	(0.03)	-0.006	(0.03)	
2nd quintile	-0.026	(0.03)	0.020	(0.03)	0.019	(0.03)	0.040	(0.03)	
3rd quintile	-0.084**	(0.03)	-0.015	(0.03)	-0.014	(0.03)	-0.001	(0.03)	
4th quintile	-0.071**	(0.03)	0.009	(0.03)	0.011	(0.03)	0.027	(0.03)	
5th quintile	-0.082**	(0.03)	0.010	(0.03)	0.013	(0.03)	0.036	(0.03)	
Global cognition									
Never smoker	0.000		0.000		0.000		0.000		0.283
1st quitile	-0.036	(0.02)	-0.003	(0.02)	-0.005	(0.02)	0.002	(0.02)	
2nd quintile	-0.041	(0.02)	0.017	(0.02)	0.015	(0.02)	0.035	(0.02)	
3rd quintile	-0.111***	(0.02)	-0.027	(0.02)	-0.028	(0.02)	-0.015	(0.02)	
4th quintile	-0.093***	(0.02)	0.006	(0.02)	0.006	(0.02)	0.022	(0.02)	
5th quintile	-0.112***	(0.02)	-0.001	(0.02)	0.001	(0.02)	0.023	(0.02)	

b=regression coefficient; SE=standard error.
Model 1: Age-adjusted.
Model 2: Additionally adjusted for education and assets.
Model 3: Additionally adjusted for alcohol volume.
Model 4: Additionally adjusted for self-rated health and self-reported medical history.
All models also adjusted for centre and measurement wave.
Far-right column: p-value is for interaction smoking*centre for the fully adjusted model.
Reference group is never smoker (zero pack years).
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table XI-2 Results from regression analyses of pack years of smoking quintiles and cognitive scores in women (n=14,238)

	Model 1: Age-adjusted		Model 2: Education, assets		Model 3: Alcohol intake		Model 4: Health measures		
	b	SE	b	SE	b	SE	b	SE	p-value
Word recall									
Never smoker	0.000		0.000		0.000		0.000		0.592
1st quintile	0.061*	(0.03)	0.023	(0.03)	0.010	(0.03)	0.012	(0.03)	
2nd quintile	0.029	(0.03)	0.040	(0.03)	0.033	(0.03)	0.035	(0.03)	
3rd quintile	-0.012	(0.04)	0.019	(0.03)	0.010	(0.03)	0.015	(0.03)	
4th quintile	0.034	(0.04)	0.069	(0.04)	0.057	(0.04)	0.062	(0.04)	
5th quintile	-0.017	(0.05)	-0.002	(0.05)	0.002	(0.05)	0.008	(0.05)	
Verbal fluency									
Never smoker	0.000		0.000		0.000		0.000		0.024
1st quintile	0.129***	(0.03)	0.092***	(0.03)	0.080**	(0.03)	0.080**	(0.03)	
2nd quintile	0.007	(0.03)	0.021	(0.03)	0.014	(0.03)	0.015	(0.03)	
3rd quintile	0.028	(0.04)	0.059	(0.04)	0.050	(0.04)	0.054	(0.04)	
4th quintile	-0.012	(0.04)	0.018	(0.04)	0.006	(0.04)	0.009	(0.04)	
5th quintile	0.185***	(0.05)	0.199***	(0.05)	0.201***	(0.05)	0.207***	(0.05)	
Letter search									
Never smoker	0.000		0.000		0.000		0.000		0.326
1st quintile	0.042	(0.03)	0.013	(0.03)	0.005	(0.03)	0.005	(0.03)	
2nd quintile	-0.069*	(0.03)	-0.061	(0.03)	-0.065*	(0.03)	-0.063*	(0.03)	
3rd quintile	0.031	(0.04)	0.055	(0.04)	0.051	(0.04)	0.056	(0.04)	
4th quintile	-0.032	(0.04)	-0.002	(0.04)	-0.007	(0.04)	-0.002	(0.04)	
5th quintile	-0.030	(0.05)	-0.018	(0.05)	-0.008	(0.05)	-0.003	(0.05)	
Delayed recall									
Never smoker	0.000		0.000		0.000		0.000		0.154
1st quintile	0.068*	(0.03)	0.037	(0.03)	0.026	(0.03)	0.028	(0.03)	
2nd quintile	0.034	(0.03)	0.043	(0.03)	0.036	(0.03)	0.039	(0.03)	
3rd quintile	-0.020	(0.04)	0.005	(0.04)	-0.004	(0.04)	0.001	(0.04)	
4th quintile	-0.032	(0.04)	-0.004	(0.04)	-0.017	(0.04)	-0.010	(0.04)	
5th quintile	0.000	(0.05)	0.012	(0.05)	0.013	(0.05)	0.017	(0.05)	
Global cognition									
Never smoker	0.000		0.000		0.000		0.000		0.351
1st quintile	0.075***	(0.02)	0.041*	(0.02)	0.030	(0.02)	0.031	(0.02)	
2nd quintile	0.000	(0.02)	0.011	(0.02)	0.005	(0.02)	0.007	(0.02)	
3rd quintile	0.007	(0.03)	0.034	(0.03)	0.027	(0.02)	0.031	(0.02)	
4th quintile	-0.010	(0.03)	0.020	(0.03)	0.010	(0.03)	0.015	(0.03)	
5th quintile	0.035	(0.04)	0.048	(0.04)	0.052	(0.04)	0.057	(0.03)	

b=regression coefficient; SE=standard error.
Model 1: Age-adjusted.
Model 2: Additionally adjusted for education and assets.
Model 3: Additionally adjusted for alcohol volume.
Model 4: Additionally adjusted for self-rated health and self-reported medical history.
All models also adjusted for centre and measurement wave.
Far-right column: p-value is for interaction smoking*centre for the fully adjusted model.
Reference group is never smoker (zero pack years).
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix XII. Selected analyses of smoking and cognitive function by centre

Due to the presence of significant interactions between centre and smoking measures in men for the letter cancellation test, and in women for verbal fluency and delayed recall, results stratified by centre are shown in Table XII-1 and XII-2 for men and women, respectively.

Table XII-1 Regression estimates of smoking status and mental speed in men stratified by centre

	Model 1: Age-adjusted		Model 2: Education, assets		Model 3: Alcohol intake		Model 4: Health measures	
	b	SE	b	SE	b	SE	b	SE
Letter search								
Smoking status								
Czech towns (n=2,547)								
Never smoker	0.00		0.00		0.00		0.00	
Current smoker	-0.13**	(0.05)	-0.02	(0.05)	-0.03	(0.05)	-0.01	(0.05)
Former smoker	-0.04	(0.05)	0.01	(0.04)	0.01	(0.04)	0.05	(0.05)
Novosibirsk (n=3,051)								
Never smoker	0.00		0.00		0.00		0.00	
Current smoker	-0.28***	(0.04)	-0.14***	(0.04)	-0.13**	(0.04)	-0.12**	(0.04)
Former smoker	-0.10*	(0.05)	-0.06	(0.04)	-0.05	(0.04)	-0.03	(0.04)
Krakow (n=3,689)								
Never smoker	0.00		0.00		0.00		0.00	
Current smoker	-0.13**	(0.04)	-0.01	(0.04)	-0.01	(0.04)	0.00	(0.04)
Former smoker	0.04	(0.04)	0.09*	(0.04)	0.09*	(0.04)	0.10*	(0.04)
Kaunas (n=3,101)								
Never smoker	0.00		0.00		0.00		0.00	
Current smoker	-0.26***	(0.04)	-0.13**	(0.04)	-0.13**	(0.04)	-0.11**	(0.04)
Former smoker	-0.16***	(0.04)	-0.09*	(0.04)	-0.08*	(0.04)	-0.06	(0.04)
Pack years of smoking								
Czech towns (n=2,431)	-0.002	(0.00)	-0.000	(0.00)	-0.000	(0.00)	0.000	(0.00)
Novosibirsk (n=2,993)	-0.004***	(0.00)	-0.002**	(0.00)	-0.002*	(0.00)	-0.002*	(0.00)
Krakow (n=3,557)	-0.001	(0.00)	0.000	(0.00)	0.001	(0.00)	0.001	(0.00)
Kaunas (n=3,048)	-0.005***	(0.00)	-0.003***	(0.00)	-0.003**	(0.00)	-0.002**	(0.00)

b=regression coefficient; SE=standard error.
Model 1: Age-adjusted.
Model 2: Additionally adjusted for education and assets.
Model 3: Additionally adjusted for alcohol volume.
Model 4: Additionally adjusted for self-rated health and self-reported medical history.
All models also adjusted for measurement wave.
For analyses of smoking status reference group is never smoker.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table XII-2 Regression estimates of smoking status and cognitive scores in women stratified by centre

	Model 1: Age-adjusted		Model 2: Education, assets		Model 3: Alcohol intake		Model 4: Health measures	
	b	SE	b	SE	b	SE	b	SE
Verbal fluency								
Czech towns (n=2,989)								
Smoking status	0.00		0.00		0.00		0.00	
Never smoker	-0.03	(0.05)	0.01	(0.04)	0.01	(0.04)	-0.01	(0.04)
Current smoker	0.07	(0.04)	0.08*	(0.04)	0.08	(0.04)	0.08*	(0.04)
Former smoker	0.00		0.00		0.00		0.00	
Novosibirsk (n=3,896)								
Smoking status								
Never smoker	0.00		0.00		0.00		0.00	
Current smoker	0.13*	(0.05)	0.13*	(0.05)	0.14*	(0.05)	0.13*	(0.05)
Former smoker	0.13	(0.07)	0.13*	(0.07)	0.14*	(0.07)	0.14*	(0.07)
Krakow (n=3,689)								
Smoking status								
Never smoker	0.00		0.00		0.00		0.00	
Current smoker	-0.05	(0.04)	-0.02	(0.04)	-0.04	(0.04)	-0.03	(0.04)
Former smoker	0.17***	(0.04)	0.15***	(0.04)	0.12***	(0.04)	0.13***	(0.04)
Kaunas (n=3,767)								
Smoking status								
Never smoker	0.00		0.00		0.00		0.00	
Current smoker	0.01	(0.05)	0.02	(0.05)	0.01	(0.05)	0.00	(0.05)
Former smoker	0.10	(0.06)	0.06	(0.06)	0.05	(0.06)	0.05	(0.06)
Delayed recall								
Czech towns (n=2,989)								
Smoking status								
Never smoker	0.00		0.00		0.00		0.00	
Current smoker	0.05	(0.05)	0.07	(0.05)	0.07	(0.05)	0.07	(0.05)
Former smoker	0.07	(0.04)	0.08	(0.04)	0.08	(0.04)	0.08	(0.04)
Novosibirsk (n=3,896)								
Smoking status								
Never smoker	0.00		0.00		0.00		0.00	
Current smoker	0.00	(0.05)	0.01	(0.05)	-0.01	(0.05)	-0.01	(0.05)
Former smoker	0.11	(0.06)	0.11	(0.06)	0.10	(0.06)	0.11	(0.06)
Krakow (n=3,689)								
Smoking status								
Never smoker	0.00		0.00		0.00		0.00	
Current smoker	-0.10*	(0.04)	-0.08*	(0.04)	-0.09*	(0.04)	-0.08*	(0.04)
Former smoker	0.05	(0.04)	0.03	(0.04)	0.01	(0.04)	0.02	(0.04)
Kaunas (n=3,767)								
Smoking status								
Never smoker	0.00		0.00		0.00		0.00	
Current smoker	-0.01	(0.05)	0.00	(0.05)	-0.00	(0.05)	-0.01	(0.05)
Former smoker	0.09	(0.06)	0.04	(0.06)	0.04	(0.06)	0.05	(0.06)

b=regression coefficient; SE=standard error.
Model 1: Age-adjusted.
Model 2: Additionally adjusted for education and assets.
Model 3: Additionally adjusted for alcohol volume.
Model 4: Additionally adjusted for self-rated health and self-reported medical history.
All models also adjusted for measurement wave.
Reference group is never smoker.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix XIII. Sensitivity analyses of smoking and cognitive function: Attrition

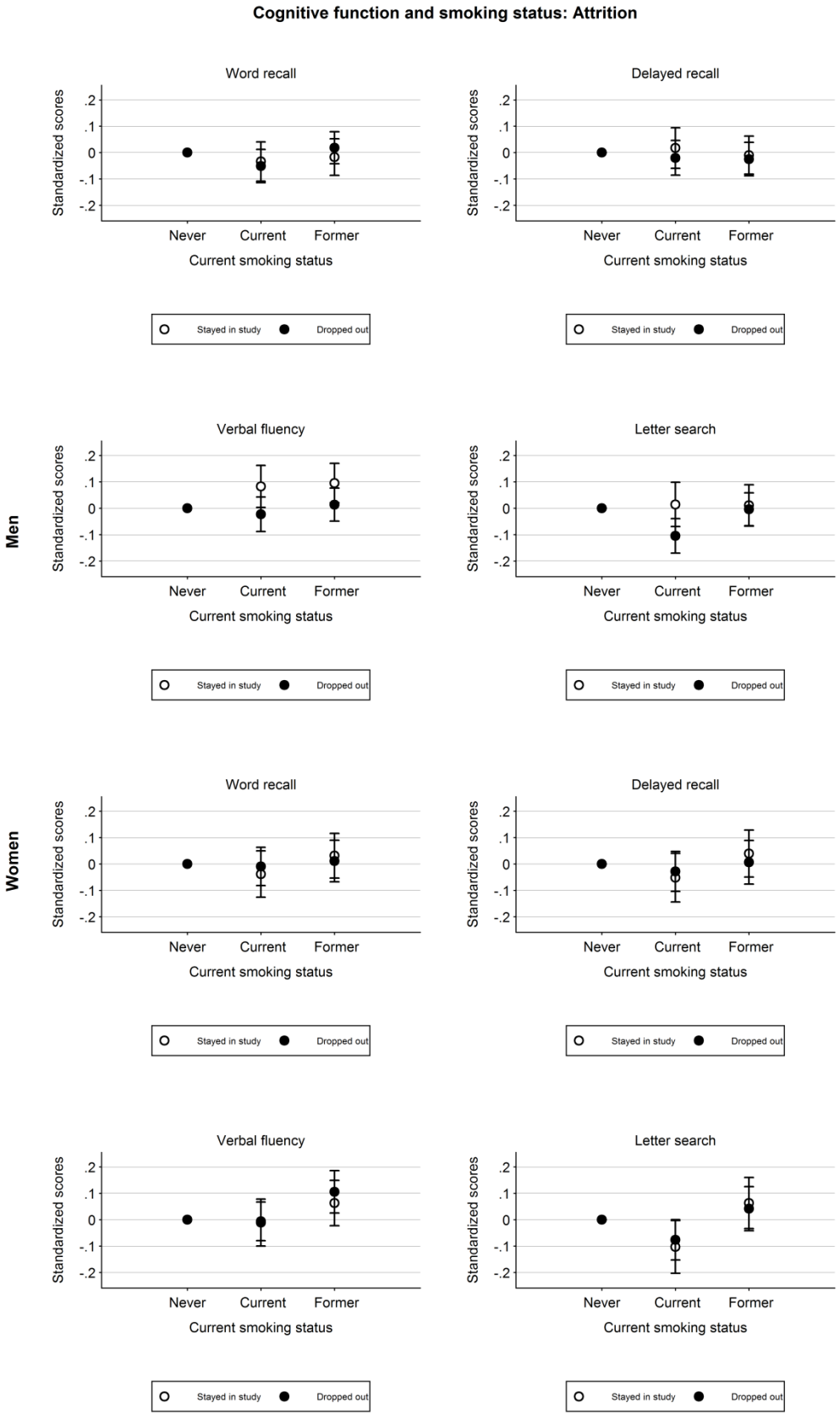

Figure XIII-1 Regression results for smoking status and cognitive function in participants who dropped out between baseline and follow-up compared to participants who remained in the study